FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY COMMITTEE

THURSDAY, MAY 19, 2011

8:00 a.m. to 4:00 p.m.

Hilton Washington DC/Silver Spring

White Oak Conference Center

8787 Colesville Road

Silver Spring, Maryland

MEETING ROSTER

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

MR. TRAN: Hello, everyone. Now, we will start the meeting. Could you please take your seats?

Call to Order and Introductions

DR. GOLDFINE: Good morning. While everybody is taking their seats, I'd like to remind everyone present to please silence your cell phones, Blackberrys, and other devices if you have not already done so. I would also like to identify the FDA press contact, Ms. Morgan Liscinsky. I know you're here, so if you could, please stand.

There she is. Okay.

My name is Allison Goldfine. I'm the acting chair of the Endocrine and Metabolic Drug Advisory Committee. I will now call the meeting of the Endocrinologic and Metabolic Drug Advisory Committee to order. We will go around the room, and please introduce yourself. We will start with the FDA and Dr. Curtis Rosebraugh to my left as we go around the table.

DR. ROSEBRAUGH: Curt Rosebraugh, Director,

Office of Drug Evaluation II.

DR. PARKS: Mary Parks, Director, Division of Metabolism and Endocrinology Products.

DR. COLMAN: Eric Colman, the deputy for Metabolic and Endocrine Drugs.

DR. CHOWDHURY: Iffat Chowdhury, clinical reviewer.

DR. IYASU: Solomon Iyasu, Director, Epidemiology.

DR. HIATT: William Hiatt, Division of Cardiology, University of Colorado School of Medicine.

DR. WEIDE: Lamont Weide, Chief of Endocrine, University of Missouri, Kansas City, Truman Medical Centers.

DR. FELNER: Eric Felner, Associate Professor of Pediatrics, Division of Pediatric Endocrinology at Emory University.

DR. BRITTAIN: Erica Brittain. I'm a statistician at the National Institute of Allergy and Infectious Diseases.

DR. GOLDFINE: I'm Allison Goldfine. I'm

head of clinical research at the Joslin Diabetes Center, Boston and associate professor, Harvard Medical School.

MR. TRAN: Paul Tran, the DFO for the Endocrinologic and Metabolic Drug Advisory Committee.

DR. SPRUILL: Ida Spruill, assistant professor of nursing at the Medical University of South Carolina in Charleston, South Carolina.

DR. GREGG: Ed Gregg from the diabetes division at the Centers for Disease Control in Atlanta.

DR. OAKES: David Oakes, Professor of Biostatistics, University of Rochester.

DR. COOPER: Bill Cooper, Professor of Pediatrics and Preventive Medicine at Vanderbilt University.

MS. KILLION: Rebecca Killion, FDA, patient representative.

DR. SMITH: Terry Smith, Professor of Endocrinology and Internal Medicine, and Professor of Ophthalmology and Visual Sciences, University of

Michigan, Ann Arbor.

DR. HECKBERT: Susan Heckbert, Professor of Epidemiology, University of Washington.

DR. VELTRI: Rick Veltri, Medical Affairs, Sanofi, and industry representative.

DR. GOLDFINE: For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are

anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you.

Conflict of Interest Statement

MR. TRAN: Good morning. The Food and Drug Administration is convening today's meeting of the Endocrinologic and Metabolic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with the federal ethics and conflict of interests law, covered by, but not limited to those found at 18 U.S.C., Section 208 and Section 712 of the federal Food, Drug, and

Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with the federal ethics and conflict of interest laws. Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the Food, Drug, and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts, when necessary, to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as

well as those imputed to them, including those of their spouses or minor children, and, for the purpose of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the findings of the action to control cardiovascular risk and diabetes lipids, ACCORD Lipid trial, as they relate to the efficacy and safety of the approved new drug application, NDA2224, Trilipix, fenofibric acid delayed-release capsule, manufactured by Abbott Laboratory. This is a particular matters meeting during which specific matters related to the ACCORD Lipid trial and Trilipix will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and

temporary voting members to disclose any public statement that they may have made concerning the product at issue.

With respect to the FDA-invited industry representative, we would like to disclose that Dr. Enrico Veltri is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Veltri's role at this meeting is to represent industry in general and not any particular company. Dr. Veltri is employed by Sanofi-Aventis.

With regard to the FDA guest speaker, the agency has determined that the information to be provided by the speaker is essential. The following interests are being made public to allow the audience to objectively evaluate any presentation and/or comments made by this speaker. Dr. Henry Ginsberg has acknowledged that he is a co-investigator of a clinical study involving lipoprotein, metabolism, during anacetrapib therapy, sponsored by Merck.

In addition, Dr. Ginsberg received

consulting fees from Merck, Bristol-Myers Squibb, Pfizer, Novartis, Sanofi-Aventis, and GlaxoSmithKline. Lastly, Dr. Ginsberg is also a scientific advisor for Merck, Glaxo, and Pfizer. As a speaker, Dr. Ginsberg will not participate in committee deliberation nor will he vote. Dr. Ginsberg is employed with Columbia University.

We would like to remind members and temporary voting members that if the discussion involves any other products or firms not already on the agenda for which the FDA participant has a personal and imputed financial interest, the participants needs to exclude themselves from such involvement, and the exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationship that they may have with the firm at issue.

Thank you.

DR. GOLDFINE: We're just going to let our final panelist member sit down and introduce himself.

DR. KAUL: Good morning, Sanjay Kaul. I'm a cardiologist at Cedars-Sinai Medical Center in Los Angeles.

DR. GOLDFINE: We're glad your flight got in on time.

I would now like to proceed with the FDA opening remarks from Dr. Eric Colman. I'd like to remind the public observers at this meeting, that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Introduction/Background

DR. COLMAN: Good morning, everyone. I'd like to welcome you to today's meeting. I'd like to spend about 10 minutes providing you with some introductory information, beginning with some comments about the fibrates. There are basically two fibrates approved in the United States. Gemfibrozil was approved in 1981 and fenofibrate was approved in 1993. Fenofibric acid is actually the active ingredient of fenofibrate, so one can think of fenofibric acid and fenofibrate as

essentially the same compound. The fenofibric acid that is trade-named Trilipix was approved in 2008 and that is the drug that we will be focusing in on today.

You can see that there are numerous generic versions of gemfibrozil and fenofibrate. At this point, there are no generics for Trilipix. However, when the exclusivity on Trilipix expires, and assuming there are no pending court cases, one would envision that down the road, there will eventually be generics for Trilipix.

I want to show you, briefly, the two indications that fenofibrate has. The first is to treat severe hypertriglyceridemia. This is generally TG levels above 500. And the aim here is to reduce the risk for pancreatitis. The second indication is to improve lipid levels in patients with hypercholesterolemia or mixed dyslipidemia. And, obviously, the ultimate goal here is to reduce the risk for cardiovascular events.

Trilipix has these two indications as well. But what makes Trilipix unique among all fibrates

is it is the only fibrate that is indicated to be used in combination with a statin to reduce TG and increase HDL in patients with mixed dyslipidemia and coronary heart disease or CHD risk equivalent, who are on optimal statin therapy to achieve their LDL goal.

Now, Abbott was granted this indication because they conducted clinical trials where they demonstrated that the addition of Trilipix to a statin resulted in significant improvements in TG and HDL levels, relative to statin monotherapy. I'd also point out that this language that we ultimately arrived at is very consistent with the recommendations that you would find in the NCP APT3 guidelines, in terms of when it's appropriate to use fenofibrate.

You will hear shortly from Dr. Ginsberg, details of the ACCORD Lipid study, so I just want to spend a couple of minutes mentioning some general aspects of the trial. This was a randomized double-blind, placebo-controlled, add-on trial. All subjects were treated with simvastatin

background therapy. Half received placebo; half received fenofibrate.

The primary outcome was major cardiovascular events, or MACE, defined as CVD death plus non-fatal MI and strike. Over 5,000 subjects with type 2 diabetes took part in the study and the mean follow-up was almost five years.

In the primary outcome, treatment with fenofibrate plus simvastatin was associated with an 8 percent reduction in the relative risk for MACE, compared with placebo and simvastatin. This difference, however, was not statistically significant. There were a number of pre-specified subgroup analyses that were conducted on the primary outcome, and there are two where the unadjusted interaction p value suggested treatment heterogeneity.

The first is gender, where you can see that there was a suggestion of benefit in men treated with fenofibrate, but there was a suggestion of harm in women treated with fenofibrate. The second subgroup of interest is determined by baseline TG

and HDL levels.

So we had two groups here, individuals who were in the highest tertile for TG and the lowest tertile for HDL. That was one group, and all other subjects comprised the other group. And, again, the unadjusted interaction p value of .06 may suggest that the treatment differences between these two groups are statistically significant. And, obviously, we will be spending a lot of time today talking about interpretation of these findings. Are they valid? What do they mean? What don't they mean? So we will be spending a good amount of time on these subgroup analyses.

This is an outline of today's agenda. The first speaker will be Dr. Henry Ginsberg from Columbia University. He was one of the principal investigators for the ACCORD Lipid trial.

Following his talk, Abbott Laboratories and their consultant, Dr. Peter Jones, will present. After lunch, you will hear from three FDA reviewers, Drs. Borders-Hemphill, Hampp, and Chowdhury. There will be an open public hearing,

and then we will conclude with the panel addressing discussion points and two questions.

I'll quickly run through these discussion points. The first has to do with providing your interpretation of the overall efficacy results from ACCORD Lipid as they relate to the Trilipix indication for coadministration with a statin. The second and third discussion points relate to the subgroups I mentioned, based on gender and based on baseline TG and HDL levels.

The fourth and fifth discussion points have to do with safety and risk benefit of Trilipix when used with a statin in this particular indicated population.

The two voting questions that you see here look a little bit different than what you saw in the FDA background document. The first question is taking into account all relevant data and levels of evidence. Should FDA require the conduct of a clinical trial designed to test the hypothesis that in high-risk men and women at LDL goal on a statin with residually high TG and low HDL, that add-on

therapy with Trilipix versus placebo significantly lowers the risk for MACE. So you'll be asked to vote yes or no and then provide the rationale for your vote.

The second question is which regulatory action do you recommend FDA take regarding Trilipix indication for coadministration with a statin. And I won't read these, but it's basically, allow continued marketing without much change, withdraw, the approval of Trilipix indication for coadministration with a statin. This is not withdraw the drug. This is to withdraw a specific indication. The drug has three indications. This is an initiative withdrawing one indication.

Then third is to allow continued marketing, but make changes to the Trilipix labeling based on the principal findings from ACCORD Lipid. And, again, you'll be asked to vote for one of these three options and provide the rationale for your recommendation.

I want to remind the committee that today's discussion will influence not only the statin

coadministration indication for Trilipix, but it will also influence the division's approval standards and regulatory policy for combinations of statins and fibrates in general.

Prior to the publication of ACCORD Lipid, we had a number of companies who expressed interest in obtaining approval of statin fibrate products, based on changes in triglyceride and HDL levels alone. And finally, another reminder that as of today there are no generics of Trilipix, but when the exclusivity on Trilipix expires, and assuming there are no ongoing court cases that are challenging the patent or exclusivity, it's very likely that down the road, there will be generics of Trilipix. And the generics carry each and every one of the indications that the innovator has.

So that's my introduction for you.

DR. GOLDFINE: Thank you, Dr. Colman. We would now like to proceed with our guest speaker's presentation, Dr. Henry Ginsberg.

While he's coming to the podium, I would like to remind public observers at this meeting

that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel. I'd also like to remind Dr. Ginsberg about our timeline.

Guest Presentation – Henry Ginsberg

DR. GINSBERG: Good morning. It's a pleasure to be here. The ACCORD trial was begun in a planning stage in 1999. And as someone who was involved for the next 10 plus years and is still involved, I feel it's very important. And I thank the committee, the FDA, for allowing me to represent the ACCORD investigators and to present these data.

You heard about my conflicts. There may be a few more here that was mentioned. In particular, as you know, Abbott and Merck provided fenofibrate. And by the way, we use fenofibrate, not fenofibric acid, although, as Eric said, it's the same molecule, but just for a slight point of clarification. And Merck provided simvastatin. I've had relationships with both companies over the

years.

I presently have, as was mentioned, a research grant for Merck to study a totally different drug, anacetrapib, at a mechanistic level. And Abbott has provided funding for a renal substudy on the ACCORD patients, and I'll show you some of those data.

I'd like to make some clarifications related to my role here. All the data I will present has been provided by the ACCORD coordinating center. Most of the data I will present have been published in our original paper or have been presented by myself or my colleague, Marshall Elam the last American Heart Association.

Some of the data I will show will be presented next month at the American Diabetes Association. There will be limited but important unpublished and unpresented data being shown with the approval of the ACCORD steering committee. I am presenting these data as an expert in lipid metabolism and treatment and as an ACCORD investigator. I am not presenting these data as an

official representative of the ACCORD investigators. That would have taken several more months of vetting by the steering committee, although they know, and have seen these data, and, in essence, approve of what I'm going to present.

However, having said that, interpretation and conclusions drawn from these data will be mine, and there might always be some differences of opinions amongst the ACCORD investigators about interpretations of some data.

Because this is an endocrine group, I noticed that anyone who is a member of the lipid mafia is no longer present at this meeting today, and I thought it would be helpful to present a little bit of lipid background. And I want to thank Dr. Colman for giving me five extra minutes to keep me on schedule.

So this is a young man, and I realize everything is relative in real life. He's had an MI. He's hypertensive. He's almost obese. He has diabetes. And he has a pretty bad lipid profile, an LDL of 140, a little bit above the mean for

Americans, but his goal being at least 100 or even less than 70, depending on your views, a triglyceride level on the top, probably 15 percent, so people with people diabetes, and an HDL down around the 25th percentile for people with diabetes or even a little bit more higher percentile than that, and a very elevated non-HDL cholesterol.

Of course, this gentleman needs to be on a statin and does a terrific job at lowering his LDL. At this level of baseline, we expect his triglyceride to fall, his HDL. And just for the purpose of the discussion, not giving any HDL rise to the statin, non-HDL much better, but still well above the goal of 100. And so we're left with a very good-looking LDL within limits, a triglyceride that's still quite elevated, and HDL that's low.

So what can we do for this man? Well, let's look at the reason he has a high triglyceride and a low HDL. This is physiology 101 for lipids. He's insulin resistant. He's insulin resistant in his heart, in his liver, in his skeletal muscle, in his pancreas, and in his adipose tissue. And that's

where I'm going to focus. And with insulin resistance in adipose tissue, he doesn't store energy efficiently. It's released as fatty acids, which go to the liver, among other tissues, but a lot of it goes to the liver, where it's made into triglyceride.

The liver can secrete that triglyceride as a very low density lipoprotein, and I've spent my life studying this process. The liver is also receiving a lot of insulin signaling. Although it's insulin resistant on the carbohydrate side, it's insulin sensitive on the lipid synthesizing side. And so it turns glucose into triglyceride and another reason to put out more VLDL. So he's hypertriglyceridemic.

Once he's hypertriglyceridemic and has more VLDL particles, he'll have a lower HDL cholesterol and a small dense LDL. And that's because of a protein called cholesteryl ester transfer protein, which has some ability to move lipids from the center of a VLDL into HDL and LDL, and return for their cholesteryl ester. And in essence, you end

up with a low HDL, a cholesterol-enriched VLDL, and you end up with a small dense LDL, which may or may not be worse than a regular LDL.

But, in general, what I'm trying to point out here is this is a triad of lipid abnormalities and we'll focus on the triglyceride and the HDL components in the presentation today. And it's driven by his underlying insulin resistance and type 2 diabetes. And everyone in the ACCORD trial was a type 2 diabetic, and we assume almost all of them, therefore, are insulin resistant.

So after you treat a patient like this with a statin, and now you want to affect the rest of the lipid profile, what's available? And we have several agents that are available: the fibrates, niacin, Omega-3 fatty acids, and TZDs, and pioglitazone being the one that actually has effects on triglyceride and HDL. And of course, we're focusing today on fibrates, which are PPAR-alpha agonists, and I won't discuss that any further.

But I would point out that based on many

years of investigation, mostly at the pre-clinical level, but with a significant number of studies at the clinical level in humans, in-vivo studies, we think that the reason that fibrates lower triglyceride are because they increase the production of an enzyme, lipoprotein lipase, which takes the triglyceride out of the VLDL, reduce the production of a protein we call Apo C-3, which blocks lipoprotein lipase activity. Maybe they affect the oxidation of fatty acids in the liver. So instead of becoming triglyceride, that turns into CO2 and water. The evidence for that in humans is minimal to nil.

On the HDL side, in addition to lowering triglyceride and having beneficial effects on HDL, there's some evidence that PPAR-alpha agonists like fibrates increase the production of Apo A-1. So on the basis of a long literature, they do the things we'd like the drug to do to people with high triglyceride and low HDL cholesterol.

In small studies, with people who have triglyceride levels typically in the 200, 300, 400

range and HDL levels in the 30s or below, the addition of a fibrate reduces triglycerides quite dramatically, increases HDL in a very solid range, and has variable effects on LDL, which we won't talk about.

So I've added fenofibrate to the statin in this gentleman, and, again, making life easy, I haven't effected his LDL, but I've dropped his triglyceride 25 percent, and I've raised his HDL about 15 percent, and his non-HDL is now almost at goal. But, of course, the big question is, do fibrates reduce cardiovascular events in this man or in people with type-2 diabetes?

So, historically, we have several fibrate trials. They started back in the 1970s with clofibrate as one of the components of the coronary drug project, the secondary prevention trial in men. And clofibrate had about a 9 percent, but not significant, benefit of non-fatal MI and fatal CVD events.

At the same time, a very large trial with clofibrate done mostly in Europe -- that was the

World Health Organization study, and that was a beneficial outcome in terms of the cardiovascular endpoints, but there was an increase in total mortality and association with GI cancer, death, and also gall bladder disease, and increased surgical deaths. And so a shadow fell over that drug.

Then a decade later, the Helsinki Heart Study was a primary prevention trial of about 4,000 men in gemfibrozil versus placebo. Remember, this was at a time where no one was getting aspirin. No one was getting ACE inhibitors. No one was getting beta blockers, certainly not in primary prevention and no one in this trial was on a statin, certainly.

This trial was very positive for the common endpoints. There were about a few hundred people with type 2 diabetes in this study. And clearly, the statistics were not really very valid, but they had the same trend as the rest of the people in the trial. A decade later, we have the VA-HIT study, the VA-HDL intervention trial, also with

gemfibrozil, 2400 men, secondary prevention.

This was a positive outcome, about a 22 percent benefit. People with diabetes, about 25 percent of the individuals in this trial had diabetes. They had the same relative benefit, but their event rates were higher, both in the placebo group and in the treatment group. This was an interesting trial, and I'll get back to it later.

But the triglyceride levels were not different from the ACCORD trial, but they had a cutpoint of HDL less than 40 to get into the trial. And the mean baseline HDL was 32. There was a modest rise in HDL, but a very positive outcome.

In Europe, at about the same time, we had a drug that we don't have here, bezafibrate. And this was the Bezafibrate Infarction Prevention trial. This was 3,000 individuals, secondary prevention, mostly men, and this was a negative outcome.

Then finally, the FIELD trial. And these two, the bezafibrate and the FIELD, were completed and published after we designed the ACCORD trial.

The FIELD trial, 10,000, just about, people with diabetes, mostly primary prevention, two-thirds men, one-third women, 11 percent reduction or lower, primary outcome which was non-fatal MI and CVD death. Also, I'll point out, some modifications of our protocol.

So, in sum, at this point in time, this was completely a study with only type 2 diabetics, very few diabetics. And in the BIP trial, 25 percent here and very few limited numbers beyond that. Overall, a mixed picture. There is a suggestion that gemfibrozil might be different than fenofibrate or the population -- the populations all differ. It's hard to really say anything very conclusive.

So we went on. Based on the latest trial that we had at the time, the VA-HIT trial, where no one was on a statin, it was just placebo versus gemfibrozil, we designed the lipid arm of the ACCORD trial. And, of course, the question was where the combination therapy with a statin plus a fibrate would reduce cardiovascular disease

compared to statin monotherapy in people with type 2 diabetes at high risk for CVD. This was the first trial looking at fibrate on top of statin, or looking at any other lipid agent on top of statin. At that time, this was the first trial designed to look at that question, and a multi-center trial in the U.S. and Canada.

The primary outcome, as you heard, was major cardiovascular events, non-fatal MI, non-fatal stroke, and cardiovascular death. And 5518 of the overall 10,024 participants in the ACCORD trial were randomized into the lipid arm. And we had very good power to see a 20 percent reduction with an estimated event rate -- and I'll point this out now, and I'll get back to it -- of 2.4 percent with about a five and a half year follow-up.

I won't spend much time on this. It's all published over a year ago. I will make a few salient points, however. One is the lipid criteria for getting into this trial. And one of the most common questions I'm asked by colleagues is why did you do this study and not study dyslipidemic

individuals? Dr. Colman's already raised the question about whether there should be a trial with dyslipidemic individuals.

This was a glucose trial. The ACCORD trial was a study of intensive versus standard glucose control with two substudies, a blood pressure study and a lipid trial. And the primary goal of the trial was the glucose outcomes. And, therefore, we wanted a broad population of people with type 2 diabetes so that any results could be extractable in the general diabetic population.

My colleagues certainly did not want to risk that goal as well as slow down the recruitment by severely limiting who could get into the trial to meet lipid criteria. And so there were some LDL criteria that were basically related to safety. You had to be over 60 or less than 180 milligrams at baseline, 180 milligrams of LDL cholesterol to get into the trial.

With HDL, we reached a compromise and we did truncate the HDL. In retrospect, that was, I think, a very important thing to do in terms of the

subgroup analysis. And so if you were a woman or you were African-American, black, you had to have an HDL of less than 55, all others less than 50. For triglycerides, there were upper levels related to safety because this was going to be a placebo-controlled trial. And so you had to have a triglyceride less than 750 on no treatment or less than 400 on an existing treatment to get into the trial. And, of course, that couldn't be a fibrate. And we did not have a lower-level cutpoint to get into the trial. People were in this trial with triglycerides less than 100 milligram per deciliter at baseline, especially the non-white population that we had.

For most of the trial, there were two modifications in the protocol that aren't relevant because, over the last five years or six years of the trial, everyone was on either 20 or 40 to get their LDL below 100, and the mean was 80 in both arms. There are only 2 or 3 percent of individuals with an LDL over 100 at the end of the trial.

We started out with 160 milligram of the

fenofibrate version that was available at the time, and I'll show you the next few slides. Because of data that came out after our trial started from two other fenofibrate trials, a trial called DAIS and a FIELD trial related to creatinine increases, we made a modification and we put a titration in the trial so that some individuals could end up on 54 milligrams per day, based on an estimated GFR. And our mean follow-up was not as long as we had hoped, for a variety of reasons. It was 4.7 years.

So in the supplemental part of our New England Journal publication, among many sections, there's one about titration of the mass medication. You had to have a GFR over 30 to get into the trial, an estimated GFR. If you were over 50, you received 160 milligram per day of fenofibrate or matching placebo. And if you were between 30 and 50 during the trial at any time and confirmed, you were reduced to 54. If you dropped to less than 30, an estimated GFR of less than 30 mls per minute per meters squared, per 1.73 meters squared body surface, you were taken off the drug completely.

And that, again, could be placebo or fenofibrate.

This was all done by the coordinating center investigators who were blinded. And remember, this was a very old, longer-duration diabetic population with multiple cardiovascular risk factors. And we assumed and expected that renal function would deteriorate across the duration of the trial.

So these are data at the end of the trial. About 15 percent of these participants were on a reduced dose of mass medicine who happened to have been randomized to fenofibrate, twice as much as was seen in the placebo group. So you can assume these people had the normal progression, unfortunately, of their renal dysfunction, associated with diabetes and other risk factors. But there was a doubling of people reaching that estimated GFR of 50 during the trial.

You can also see that, not on mass medication, 22 percent in the feno group, 18 percent, so less of a difference in the placebo group and not on mass medication because of a low GFR, less than 30, 66 versus 30 between fenofibrate

and placebo.

So clearly there were affects of the drug on creatinine and FR and estimated GFR. And what we do know is, looking at those on reduced dose during the trial, it had no effect on outcome, other than the fact that those people who had reduced dose had about a 30 percent higher event rate. So dropping your GFR during the trial and going on a reduced dose probably indicated you had more vascular disease or diabetic complications, and you had a higher event rate. But the effect of fenofibrate in that group was, if anything, slightly better.

These are not numbers that I would use statistically, obviously. But, clearly, there was no difference between the efficacy or lack of efficacy of fenofibrate in that group. The event rate -- the hazard ratio in the group on reduced dose fenofibrate was .82 versus .93 on those not on reduced dose. In addition, those on reduced dose had only slightly less efficacy in terms of lipid changes, compared to the group on the full dose.

I'll move on from there. So baseline

characteristics -- again, I'll only spend time on the lipid side, and 60 percent of the subjects at baseline were already on a statin, so baseline LDL was 101. HDL was 38. It was 36 for men and 41 for women, and that was due to our truncation of 50 and 55. So we did end up with a lower HDL group but clearly not like the group they had in VA-HIT.

In triglyceride levels, the median of 162, that's probably about the 70th percentile for the general population and a lower level than that for the diabetic population, but clearly not a very hypertriglyceridemic group overall.

What about the safety, which is one of the issues that you're going to discuss? And of note, if you're using a criteria of out of the ordinary, severe muscle aches and pains any time during the trial, 40 percent of the individuals had that complaint at some point during the trial, whether they were on placebo or on fenofibrate. And when you look at the association of that symptomatology with CK levels, CK above five times the upper limit of normal, no difference in very, very, very few

people, 10 times the upper limit of normal, almost no one.

So we really had no evidence of severe myocitis, no evidence, clearly, no events of rhabdomyolysis on fenofibrate plus simvastatin 20 or 40 in this trial. Some of the things that popped up in the FIELD trial, too, were pulmonary embolism and pancreatitis. We saw no cases of either of those, or no differences, certainly, during our trial. And if you look at other serious AEs, there were no differences between the groups.

In terms of liver function tests, ALT is greater than three times the upper limit of normal, a little over 1 percent, 1 and a half percent in each group with no difference. ALT greater than five times the upper limit of normal, very low rates, but a slight insignificant increase in the fenofibrate group, and that's been reported.

Of interest, we looked at women who elevated their serum creatinine to greater than 1.3, or men to greater than 1.5 milligram per deciliter during the trial. So this was incident elevations of

serum creatinine above these arbitrary cutpoints set by our data safety monitoring board, actually. And in the placebo group, it was about 19 percent for the men and the women. And in the fenofibrate group, it was 28 percent and 37 percent for the women and the men, respectively. So, clearly, as had been reported about a third of the way through our trial, fenofibrate raises serum creatinine.

In addition, though, when we look at the -- this is a combination of incidence and prevalence, unfortunately, the way this was described. But having microalbuminuria anytime during trial was 38 percent on feno and 41.6 percent on placebo, actually a significantly lower rate of microalbuminuria.

In addition -- and most of you can't see this -- there was a significantly lower rate of about 15 percent or so of macroalbuminuria. So while creatinines were going up more, there was less of a presence of, anytime during the trial, micro or macro albuminuria.

I would just like to spend a moment on the

creatinine issue. And these are data from our trial, showing that within four months of the addition of feno or placebo, the group on feno raised their creatinine, and then over the course of the study, had this gradual rise which paralleled the rise in the placebo group. Of course, there was no immediate rise in the group receiving placebo.

With funding from Abbott, we did a study after the end of the trial, where we brought back three groups of individuals eight weeks later. And the groups were defined as fenofibrate cases. Those were individuals who raised their creatinine more than 20 percent during the trial. We had fenofibrate controls. Those are individuals whose creatinine went up less than 2 percent on fenofibrate during the trial. And then we had placebo controls.

So this was a bit of a sampling that was who was available, who agreed to it, based on some criteria, but not the entire cohort by any means. And the points of interest are that, at baseline,

there were some differences between the groups based on chance in the small numbers, but the feno cases at baseline had an estimated GFR of about 97, the controls were about 89, and the placebo about 93. And you can see at four months, the feno cases, because their creatinine went up, their estimated GFR dropped quite dramatically, no change in the feno controls, no change in the placebo controls.

At the trial closeout, the 97 mls per minute in the feno cases was down to 72, and then the feno controls went from 88.6 to 80, and the placebo controls from 93 to 83. So these two groups, or at least the placebo group, the natural course of their renal disease over their time in the trial, but clearly an effect on estimated GFR in the group whose creatinine went up.

But the key data are shown in the next slide. Eight weeks after cessation of fenofibrate, this group had increased their estimated GFR to 83.5. The placebo group didn't change, and the feno controls actually went back to 90.

We're not sure what to make of this. They didn't raise their creatinine initially. They probably had better renal function, and so maybe this is the natural cause of a subgroup of individuals. Some might say it's an effect of fenofibrate on the beneficial side. I think the key data are right here. Whatever happened during the trial to creatinine was completely reversible and the two groups, the placebo and the feno cases, matched at the end of the trial.

These data are very, very similar to those in the field trial. These are their creatinine data. They actually had a run-in with everybody on fenofibrate for several weeks. Then they were randomized to feno or placebo. And at the end of the trial, they brought back, I think it was, 600 participants, and they saw a complete reversal of the creatinine rise.

In addition, when we look at microalbuminuria, macroalbuminuria, end-stage renal disease, a change in urine albumin to creatinine ratio, and for what it's worth, in a smaller number

of individuals, primary study outcome, it didn't matter if you were a fenofibrate case or not a case related to the cases having greater than 20 percent increase in creatinine at month 4 and the controls, the no FACI, having no increase. You can see that, and you can't see.

But the odds ratio -- the hazard ratio between those groups is .94, which is the same as the overall study. So even having a creatinine elevation for, on average, about five years, didn't seem to affect the outcome in terms of cardiovascular events. It was associated with a little bit less, but significantly so micro- and macroalbuminuria.

Let's move onto the lipids. And, again, this is from the paper. And the point is here that we had good matching of LDL cholesterol with everyone close to 80 the last several years of the trial. If we looked at HDL, those on feno had an immediate rise by four months and pretty much steady after that, with a gradual rise in the placebo group over time, narrowing the difference

between the two.

The triglycerides are quite dramatic, an immediate drop in TG on fenofibrate, and then stability, and a gradual fall -- I'm sorry -- fall with stability and a gradual fall over time in the placebo group.

This is a little blurry. I'm sorry. I just took it out of the supplemental data just to show that for HDL -- and this is the feno group -- very, very consistent across all the years of the study, of about a 6 percent increase in HDL, but in the placebo group, starting out with a 2 and a half percent increase at month 4, rising to about 5 to 6 percent over time, narrowing the difference between the feno and the placebo effects.

The same thing on triglyceride, a very consistent 23 to 25 percent reduction in the feno group and a very gradual but increasing fall in TG to about 15 percent, so narrowing the difference in that group.

Why we saw this rise in HDL and a fall in triglyceride over the course of the study is not

clear. There's always some regression to the mean. There's also a study effect. Everyone in this trial had better glucose control than before they came in the trial. They were on other medicines, probably to a greater extent. And we'll never fish this out, but it's an interesting finding, and it shows why short-term studies often exaggerate the efficacy of drugs, at least versus a placebo group that's in a very intensive study; and how to relate that to real life of course is not that easy.

You know the primary outcome. The only point I'll make here is that we estimate a 2.4 percent event rate in the placebo group. It was 2.41. This study was not underpowered. Unfortunately, the effect was underpowered with only an 8 percent reduction in the primary outcome.

Secondary outcomes, including the primary outcome divided into its components, I only point out two of them, total mortality, the hazard ratio, was .91, so there was no evidence of an increased mortality as there had been in some fibrate trials; cardiovascular mortality .86, neither of those

being significant, but both on the right side, or at least similar to the overall outcome. And except for stroke, where there was really no signal at all, all the others were in that about 8 to 12 percent lower side in terms of potential feno benefit, but nothing, of course, statistically significant.

Now, let's move onto the subgroups. And I want to make the point that in -- and this is another section in our supplemental data. These subgroups, almost all of them were chosen specifically, the typical subgroups -- age, gender, race, they were chosen at the start of the trial and written into either the mop or the sop. I never remember which one. And it was written in the protocol at the beginning of the trial that we would look at subgroups across the range of lipids. We did not, at time zero, decide how we would cut up the lipids.

With about six months to go in the trial and everything obviously still blinded, we decided that we needed to make that final decision. And so it

came down to above and below the median, or tertiles, or quartiles, and we chose tertiles, for LDL, HDL and triglyceride. We also added this rather unique tertile combination of an upper tertile triglyceride and lower tertile HDL because the FIELD trial investigators had published by then their paper on metabolic syndrome criteria, where they used about a TG of 200 and an HDL less than 40 to define people with metabolic syndrome, and they showed a significant benefit in that group.

So we decided not to be as arbitrary -- and I don't mean to denigrate the FIELD investigators at all on that point -- but to stick with our tertiles. And we ended up with sort of similar lipids, as you know, maybe a lower HDL. So all of this was pre-specified when we were all blinded to the outcomes.

And you saw -- Dr. Colman presented these data, and I just want to go over them again, but first some points, just to remind everybody, because you need this; if you can keep this in your mind. The placebo event rate for the whole trial

over 4.7 years was 11.3 percent. Obviously, older people did worse. Non-whites -- and we had about 30 percent non-whites -- they had a lower event rate than whites on placebo. As expected, the primary prevention group had an event rate of 7.3 percent. The secondary prevention group, which made up about 37 percent of the participants, had an 18 percent event rate.

So there are some obvious differences in subgroups in terms of their risk for events during the trial on placebo, as well as how they responded to feno. And here it becomes obvious. Women on placebo had an event rate of 6.6 percent versus 13.3 percent in the men. And, as you already heard, the women had more events on fenofibrate and the men had fewer events. The hazard ratio here is .82. The hazard ratio here is 1.38.

So when I looked at the primary outcome I just mentioned, .82 for men, hazard ratio of 1.38 for women, if we look at the components of that: cardiovascular death, .84, .98; non-fatal MI, .79 for the men and a hazard ratio of 1.43 for

the women; non-fatal stroke, no difference; any stroke, no difference; death from any cause, no difference.

So non-fatal MI was the basis for the higher event rates, the higher hazard ratio, and the heterogeneity that we see in women versus men. So the question is -- and I have a bunch of these, and I should say on fenofibrate. Why did women in ACCORD on fenofibrate have more non-fatal MIs than those on placebo?

Well, if we start to look at them, the women, there more non-whites. These are the whites, 60 percent versus 71 percent. And on non-whites, African-Americans and Hispanics, the vast majority of Hispanics were from my center, Columbia, or Tom Bigger's center at Columbia, where we have Dominicans who have a large Afro-Caribbean background. And African-Americans have lower triglycerides and higher HDLs than Caucasians. And they actually didn't do as well on that first subgroup analysis. They had a heterogeneity value of .08 for non-whites versus whites in response to

fenofibrate. And the non-whites had lower event rates. I did point that out.

So you end up with a lower-risk group that didn't respond as well. These people didn't respond as well to fenofibrate. Prior CVD, obviously the women, as expected, less prior CVD than the men, and so they're a lower risk group; otherwise relatively well-matched in terms of other diabetic complications and drug use.

When we look at baseline lipids by gender, no difference in total cholesterol, no difference in median triglyceride, slightly higher, in fact. LDL cholesterol to baseline, not different. HDL is as expected, different, 36.6 in the men, 41.4 in the women. And we narrowed this difference because of our truncations in HDL for an inclusion criteria.

So nothing here jumps out as to why the women might not have responded as well and had more non-fatal MIs. And if we look at lipid response, again, these men and the women -- and I have on the left of the slash the triglyceride response in

milligrams per deciliter, to fenofibrate on the right is the placebo. And this is after 48 months. So it's not the complete cohort, but everyone who had 48 months of measurements. And you can see, minus 43, minus 45, for LDL minus 16, minus 22, and for HDL plus 2, and plus 2.3. Nothing jumps out at you as a differential responsiveness to fenofibrate between the men and the women.

So why did women in ACCORD on feno have more non-fatal MIs? I don't know, at this point. They were at lower risk at baseline. They have lower event rates during the study. Their baseline lipids were similar to men, except for higher HDL, and their response to fenofibrate was similar.

Then we've looked further, and of course, once you start to cut up the pie, you're really walking on thin ice, but I think we have some at least interesting data. And so we looked at men and women divided into primary and secondary prevention, because, overall, remember the secondary prevention group had an 18 percent event rate versus about an 8 percent event rate in the

primary prevention group. And what we found was very striking.

Primary prevention, the women had about the same number of events on feno or placebo, but on the secondary prevention, women, there was a marked increase in events on feno. And that's just shown here graphically. Primary prevention, the hazard ration for the women is about 1.05. You can see very low event rates on placebo and about the same event rates, an 8 event rate difference between feno and placebo, out of 600 women in each group.

The men, primary prevention, higher event rates, a very slight lowering of event rates on feno with the hazard ratio shown here, just about 1. The secondary prevention group, the women -- and it's a small group. There are just a little over 200 women at each arm, so a little over 440 women overall who had had an event. On placebo, their event rate was 13 percent, and it was 20 percent on fenofibrate, a hazard ratio of about 1.6.

The men, about 800 in each arm. The placebo

group had a 19 percent event rate and the feno group a 15 percent event rate, and so a striking difference of about 25 percent, 20 percent, between "efficacy" for feno in this group, but clearly a bad outcome in the secondary prevention women. And this event rate of 20 percent is the highest, within confidence limits of course, but the highest of any group in the trial.

So let's look at their events, broken down individually. And what jumps out again is the non-fatal MIs. That makes up the difference, just 14 more non-fatal MIs in the secondary prevention women on fenofibrate.

So why did this happen? And if we look again at the baseline characteristics, we can see here, race is not an issue. Other factors, they're well-matched, but when you get down to complications of diabetes, much more micro- and macroalbuminuria in the secondary prevention women, much more retinopathy, peripheral neuropathy, heart failure, 13 percent versus 2 and a half percent, amputations twice as high, less TZD use, probably

because of -- maybe because of more heart failure or more concern about that, I don't know, but more beta blocker, more ACE, more calcium channel blocker use, consistent with the fact that they were very sick; more statin use in that group as well, at baseline. Again, these are all baseline. I don't have on-treatment values. So, clearly, they were a sick group of people.

If we look at the baseline lipids and just focus on the women here, the primary status women are the gray bars and the yellow bars are the secondary status women. Again, the number is over 1200 in primary and 440 or so in secondary prevention status. Triglycerides, not different; HDL, not different; LDL, not different at baseline.

If we look at response to therapy, triglyceride response in the secondary prevention women may have been less than in the primary minus 39 versus minus 28, but there was also less change in the placebo groups where the differential was the same.

But here's a striking finding, and that is

that there was really no effect on HDL fenofibrate in this secondary prevention group. And the placebo group actually went up, and the feno group didn't change at all. Otherwise, the LDL changes were fairly well matched.

So why did women in ACCORD with secondary prevention status on fenofibrate have many more non-fatal MIs? Again, I really don't know, but they were at much higher risk at baseline. They had the highest event rate during the trial. The baseline lipids were the same. They may not have responded as well to fenofibrate, and this may have been by chance. And these are the data that were published from the FIELD trial, where in the overall -- in the basic subgroup analysis, the women actually did better than the men. The interaction p was not significant, but at least the trend was there, so they have an opposite finding from our finding. And there are no other data to go by that are valuable in the literature.

So let's finish up with the dyslipidemic group, and, remember, this was a TG in the upper

tertile and in HDL in the lower tertile. This turned out to be 17 percent of our population. Arithmetically, you'd think it would be about 9 percent or 10 percent, one-third times one-third. But, remember, we truncated the HDLs to enrich this population, and low HDL and high triglyceride are linked with a correlation of about .4, so that enriched the population.

I would estimate -- and it's for your consideration -- that in the general diabetic population, there are probably 12 or 13 percent of people who would fall into this combination tertile a little more than the arithmetic would typically suggest.

The points here are that on placebo, this high triglyceride, low HDL group had a 17 percent event rate, almost as high as the secondary prevention group of 18 percent. And they dropped to a 12.4 percent event rate, and that was a 31 percent reduction. Everyone else in the trial, the other 83 percent, had a 10.1 percent event rate in both arms. Absolutely nothing happened and the

event rate was not that high.

So why were there fewer events on fenofibrate in this dyslipidemic group? Again, there were more whites in this group, and they did better than non-whites on fenofibrate. This is of interest, though. Although the event rate was almost 18 percent, almost equal to the secondary prevention group, it wasn't because of a marked enrichment in secondary prevention status. The overall was 37 percent, so a slight enrichment. So this was a very high risk group that had events as if they were really CHD equivalents. And that's a very interesting finding, from my viewpoint; otherwise, more micro- and macroalbuminuria in the high TG, low HDL group, more heart failure, and not much else happened at baseline again.

The lipids, by definition, obviously, triglycerides were much higher, and this is the median triglyceride, 285. LDLs were the same. By definition, the HDL is much lower, and really not that differential that we saw between men and women overall, which was 36 and 41. So these women look

just like the men at baseline in terms of their lipids.

What about response to therapy? Well, this is about a 25 percent response, placebo corrected. This is a 15 percent response. This is a 7 percent increase, placebo corrected. This is nothing happening. And, in general, for 87 percent of people in this trial, fenofibrate did not affect their lipids very much at all. And in the dyslipidemic group, where we see a strong suggestion of benefit, there were positive lipid effects.

So why did the dyslipidemic group do better? I can speculate that they had higher risk at baseline, slightly higher, but much higher event rates. They had, by definition, dyslipidemia. They had better responses than all others, but, of course, this still could be a finding by chance.

On the other hand, when we go back to the initial table that I showed you earlier, where we looked at several trials, when we look at the trials where post hoc subgroup analyses were done,

looking at a dyslipidemic population, in Helsinki Heart, where there was a very positive overall benefit, that doubled in a subgroup that had high triglyceride and mostly a low HDL, although some of this LDL/HDL ratio greater than 5 could have been very high LDL.

In the BIP trial, not significant overall, a 40 percent benefit if you took TG over 200, whether or not HDL was above or below 40. The FIELD trial, 11 percent overall, 27 percent in that metabolic syndrome group of TG of over 200 and HDL less than 42. And our own trial now, 8 percent overall, 31 percent. So a strong, I think, confirmation that our subgroup analysis is more than by chance.

DR. GOLDFINE: Dr. Ginsberg, I want to remind you, you have five minutes left.

DR. GINSBERG: I have five minutes?

In addition -- and this was very interesting, and I'm not sure how we'll go further than this, but we haven't poked yet. But in the dyslipidemic group, the men have a 35 percent benefit; the women have a 12 percent benefit.

Still, a suggestion within the very weak statistical limits here that there is a gender difference, but, clearly, dyslipidemic women did not look like the rest of the women in this population. And, of course, if you didn't have dyslipidemia, your hazard ratio went up a little bit if you took out that small group of dyslipidemic women. And dyslipidemic women, as I said, their lipids look just like the dyslipidemic men, and their response was the same.

So to add to that list of why the dyslipidemic group did better on feno than everyone else, they didn't demonstrate significant gender differences. And just in the last two minutes, I have three slides, I think, to talk about the ACCORD Eye study, because I do think it throws another aspect of the issue in play here that you're discussing today. And this was led by Emily Chew, and this was a study with baseline and year-four comprehensive eye exams, the outcome being a three-step progression on fundoscopic photography of retinopathy.

The bottom line here is really at the bottom of the slide, with about -- people on fenofibrate and simvastatin, irrespective of intensive or standard therapy, had about a 40 percent reduction in the progression of this retinopathy compared to those on placebo and simvastatin. Intensive glucose control had about a 30 percent benefit as well, so two arms of the trial showed independent benefit on retinopathy.

What really makes this confusing is that the retinopathy benefit was not in the dyslipidemic group, but it was in all others. But this is a substudy of a small group, so the numbers are very small here. But that does throw another kink in. And the last point to make is that although the interaction p value is .03 here, the benefit to me looked like it was all in people who had some retinopathy at baseline.

So my conclusion is, is it worth adding one more lipid-lowering drug, in this case, a fibrate, to a statin multi-drug treated patient with type 2 diabetes? Speaking for myself, I would say yes if

they have significant dyslipidemia with a TG over 200 and an HDL below 35 or maybe below 40 in women. And that's maybe a stretch of my data beyond any other stretch. And this is probably about at least 10 percent of all Caucasian diabetic population, and maybe if they have retinopathy, regardless of lipid levels. And so thank you.

Clarification Questions for Guest Speaker

DR. GOLDFINE: Thank you, Dr. Ginsberg, for your presentation. I would now like to open it for discussion and clarifying questions from the committee for the guest speaker. Go ahead.

DR. COOPER: Dr. Ginsberg, thank you. I have a question. One of the things we are being asked to do today is assess the overall risks and benefits of this medication. And I would like to get you to clarify a little bit about the renal risk.

You showed us data that suggested that 28 to 37 percent of the persons on the study drug had an increase in GFR or an increase in creatinine versus 19 in placebo. Sixteen percent had to have dose

adjustments because of changes in their GFR. And even though the GFR improved in your ancillary study when the study drug was stopped, what are the implications in terms of patients who would stay on the drug in terms of their renal risk? Is that an important thing that we need to consider as we move forward today.

DR. GINSBERG: So it was on one of those slides. There was no difference in renal failure. The definition is in the supplemental data, but certainly no one in the study, I think, went on dialysis during the trial, maybe one or two people. So there are no data there.

Overall, if you looked at the various proteinuric classifications or renal failure as a classification, there did not seem to be an adverse outcome. Certainly, the fact that it's reversible is very good news. What does that mean while it's high? The best we have are the data that I showed, that it doesn't seem to affect the cardiovascular outcome and it doesn't seem to affect the renal outcomes, other than the fact that if your

creatinine went up, you did have a greater chance of having an event, but that was true for both groups.

So there have been three or four hypotheses presented for this over the years, and very, very little mechanistic data, or few normal subjects had inulin or some other type of direct estimated creatinine clearance. The hypotheses are, based on some rodent data, that people on alpha drugs cause an increase in protein synthesis in muscle and therefore you get more creatine and you get more creatinine. We all, it turns out, secrete some of our creatinine from the tubules, and there's some data suggesting that that's blocked by PPAR-alpha agonists.

The third is -- and there's evidence for this -- that you can dilate the efferent arteriole at the glomerular so that you have an ACE-inhibitor-like effect. And ACE inhibitors raise creatinine, and everybody accepts that as being either benign or good for you. And that's my bet, because of our overall data.

DR. GOLDFINE: We have a series of questions, so if that answers yours, let's move onto Dr. Hiatt.

DR. HIATT: Two questions about your approach to the analysis of the ACCORD trial. The first is that, traditionally, you move from the analysis of the primary endpoint to the secondaries based on a primary endpoint finding.

My question is to you and the investigators, did you then choose to interpret the findings of the secondaries as informative for decision making or hypothesis generating? And my second question is, the decisions around the analysis plan occurred rather late in the process. Normally, you try to write your analysis plan before you randomize the first patient. In this situation, you made decisions quite late in the process that appear to be informed by other trials that occurred subsequent to the start of your trial.

My question is, could that lead to a biased interpretation of these secondaries, even though you were still blinded?

DR. GINSBERG: So let me -- my white flag here is that I'm not a trialist by nature. And so I go with the rest of the more professional trialists in the group. And, yes, the purest statistician would say, once you have a negative primary outcome, you don't look any further. No one does that. I've often asked, why do we do subgroup analyses when you tell me it's all useless anyway? And the answer is hypothesis generating.

So on that level, I would say all the data past the primary outcome are hypothesis generating, and we've tried to follow those up by doing even further subgroup analyses. I am a physiologist, cell biologist by nature, and I use data in the literature to both support what I think is happening and to move forward. And here I think are the two findings that we've focused on, both hypothesis generating.

One has the dyslipidemia, has historical precedent in several other studies that support it being less than chance. The gender difference does, and it has some data suggesting it is by

chance. But that's as far as I will go. I would add, as a clinician, I use fibrates for people whose TGs are 200 and above and whose HDLs are very low.

In terms of your second question, we did have -- again, at pre-randomization of the first patient, we had in the protocol that we would examine the lipid subgroups across the range of lipids. We did not determine at that point what that range would be. So the use of tertiles was sort of a roll of the dice because we didn't have any good data.

As I mentioned, the upper tertile, lower tertile combination was based on the Lancet paper. I don't know. Is that Bayesian? That we're more likely to find a positive outcome? That's beyond what I know. But we clearly did choose that extra look, based on something that was published.

DR. HIATT: So just so I understand, so you're saying in your response that it's a negative trial, but in your last slide, you're interpreting it as a positive trial.

DR. GINSBERG: No. In my last slide, I said that -- the last slide where I gave my opinion, I said that I would use this drug in people -- based on this trial, based on a hypothesis-generating result that I would use this drug the way I've always used it, because I believe that the trial suggests strongly that it works and that there's no harm in using it in that population of people. And my belief is based not only on this trial, but on several post hoc analyses of prior trials with monotherapy.

DR. GOLDFINE: Thank you.

Dr. Kaul?

DR. KAUL: Thank you. In slide 56, you speculated that the reason why dyslipidemic patients did better was because the baseline risk was higher; so was in the secondary prevention cohort as well, 18.1 percent and 17.3 in the dyslipidemic and the placebo arm. And in the former, you only had a 2 percent absolute difference, and in the latter, you had a 5 percent absolute difference.

So the baseline risk p probably is not the likely explanation for that.

DR. GINSBERG: We haven't looked -- I'm trying to think if this is logical. We haven't looked at the secondary prevention event rates according to dyslipidemia or non-dyslipidemia. My bet would be, from everything else I have up there, that a non-dyslipidemic secondary prevention patient/participant would have a significantly lower event rate than a dyslipidemic because the dyslipidemics without secondary prevention status had higher event rates.

I'd have to go back and look at that. I see what you're saying, and I'm just putting up things. I think that the best possibility is that they responded to the drug lipid-wise. Having said that, I admit that the women responded as well as the men, lipid-wise. And so I don't say anything here as it's written in stone. And I'm trying to just give you the options and some greater understanding.

DR. GOLDFINE: Go ahead.

DR. KAUL: In slide 34, when you looked at the components of the primary composite endpoint and outcomes by gender, you stated that the signal for risk in women was driven by an increase in non-fatal MI, but you did not present the confidence limits. If you had the confidence limits there, you would see it as considerable overlap. And if you did a formal test of heterogeneity, I wouldn't see that there is any heterogeneity and treatment effect across the components of the composite endpoint.

DR. GINSBERG: Right. And that's why, if I did, I apologize. I never meant to use the word "significant" in any of these post hoc further subgroup analyses. But these are explorations to try to explain a significant interaction by gender in the overall outcome. We're not powered to look at any of these individual outcomes. All I'm saying is that when you look at the hazard ratios, the data without statistical support and the absolute numbers say these are where the events were. There were no statistics to do here because

we're down at a level where there were no statistics planned and there's no statistical power.

So again, I agree with you, and I'm not making -- I'm trying to understand where the signal was. We had a significant signal in women overall. And we have some differences in dyslipidemic women and non-dyslipidemic women, which also, by interaction, probably wouldn't be significant, although it's glaring in the absolute term because there were so few dyslipidemic women. So nowhere have I, I hope, used the word "significant."

DR. KAUL: One last clarification, and this relates to what Dr. Hiatt asked.

In the design paper that was published in the American Journal of Cardiology in 2007, there were only three subgroup hypotheses stated: the treatment effect across levels of LDL cholesterol, HDL cholesterol, and triglycerides.

At what point did you think about including the dyslipidemic population? Because I thought that that would have been the most interesting

subgroup to do the analysis. The dyslipidemia hypothesis has been simmering in the spot of biological plausibility for over 20 years, since the Helsinki Heart Study first looked at it post hoc. And I thought that would have been perhaps the most interesting subgroup to look at.

DR. GINSBERG: Right. That's my fault. As I said, this is actually the first large clinical trial I was ever involved in, and because this was a trial put together by glucose and blood pressure people, there were only one or two other people who were no more experienced than I was in lipid trials.

These are the ways that these guys do this stuff. They have age, gender, race across tertiles or across the range. And I never thought of approaching the subgroups in any other way. And I have to admit, because of the VA-HIT data where the TGs were not that different, and they had a similar response to TG above and below their median, actually, we thought that despite the fact that I fought for a more dyslipidemic group, I just had

the belief overall that the study would be positive, and it just never occurred to me to do that, unfortunately.

DR. GOLDFINE: Dr. Veltri?

DR. VELTRI: Yes. Henry, I think what you started with was very important. You're trying to fit a lipid trial into, really, a diabetes trial, essentially.

Two questions. I'm a little confused about the baselines, in that it sounds like about 60 percent of these patients were on statins coming in and about 40 percent were not. And then they had a run-in period with simvastatin, but that baseline post, really randomization, wasn't known.

Is that correct?

DR. GINSBERG: Right. Everyone was put on a statin as they were enrolled. And then a month later, they were randomized to feno or placebo. So the first data we have are at four months for the entire cohort. And the only data -- we have the baseline data, which is 60-percent statin driven and 40-percent non-statin driven. That's correct.

Furthermore, the study started with an algorithm for dosing the simvastatin, based on what your baseline LDL was. There was a design that we had in place at that time, that everyone should have an LDL of 100 in that trial, and that would be very neat and nice, based on the guidelines. And then we'd look at the fenofibrate effect versus placebo. Then Heart Protection came out, and so we had to change our strategy. So we had some modifications of the trial.

So the only data that -- the only data that are a value to me is that everyone had an LDL -- the mean LDL was 80 at the end of the last several years of the trial, and it was matched between the two groups.

DR. VELTRI: The other question I have is trying to get maybe a little bit more insight into some of the other lipoprotein or inflammatory marker. I know HSCRP was looked at. Specifically, in regard to trying to look at, perhaps, were there any differences, especially in the gender issue, regarding these other markers?

DR. GINSBERG: So this study cost over $300 million and we have no other biochemical measurements at the moment. We have freezers filled with samples. I have a grant application at the NIH in response to an RFA. So we have no Apo proteins. We have no clotting factors. We have nothing else. And I clearly hope that we'll receive some funds to measure.

I mean, there are a lot of hypotheses. For instance, women have different-sized VLDL particles. Their triglyceride might go down and their Apo-B might not, wherein the men, maybe Apo-B went down. And that might differ between the dyslipidemics. So a lot of interesting things that could help us tease out further the gender difference and the difference between dyslipidemics and non-dyslipidemics, but right now, we have no funds to do any measurements.

I should mention one thing, just to go back to the renal study, and I didn't show it, but we do have cystatin levels which are considered by some to be better markers of GFR. They go up and they

come back down as well, so another marker of return of renal function to a 10-year baseline.

DR. GOLDFINE: Thank you.

Dr. Smith?

DR. SMITH: Thank you. Dr. Ginsberg, you may have just answered part of my question. But in thinking about the marked gender differences and considering the possibility of an underlying mechanism, what do we know about the estrogen status of these individuals? And if we don't have those numbers, are they retrievable?

It would seem to me that given the complexities of estrogen activities in virtually every tissue system I can think of, this would be a rather reasonable place to begin.

DR. GINSBERG: Right. We have those numbers. I wrote them down last night on the train. They were balanced between the two arms, feno and placebo. And I think it's between 5 and 7 percent of women who were on estrogen at any point in the trial, so very low hormone usage in our women.

DR. SMITH: But I'm asking a more encompassing question in dodging this estrogen status and whether fibrates, in fact, alter that level.

DR. GINSBERG: I don't know of any data about PPAR-alpha agonists and estrogen or estrogen -- the gonadal hormonal pathways. It's a little bit out of what I would read, and so I don't know. I mean, fibrates have no use in PCOS, for instance, or in irregular menses, or infertility, that I know of, but I have no data as to that regard.

Again, I don't have -- I can't give you data right now of how many women in this study were pre-menopausal. There were, I'm sure, a few, very few, because of the inclusion criteria for age. You could get into the trial under the age of 50, I think it was, if you had CVD, but that was still a very limited group. So I think almost all the women were post-menopausal and very, very few were on any hormones.

DR. GOLDFINE: Thank you. We have two final

questions. Dr. Gregg?

DR. GREGG: Yes. Just a question of clarification. For the retinopathy progression study, was this a preplanned analysis with adjustments for multiple testing or was this a standalone post hoc analysis? In other words, are those p values adjusted in any way?

DR. GINSBERG: Is anybody here? Is Emily here? Or Tim, do you have an answer for that? I can't -- I just don't remember. I'm sure on the paper, there's something about that in the paper.

This was clearly a pre-designed trial, and those numbers that I gave you, are they adjusted for any sort of comparisons? I think that they might be adjusted at least for the 2x3 design or 3x3 design, but I can't say exactly. I'm sure it's in the paper, though. Sorry.

DR. GOLDFINE: If you can find that information during one of the breaks, perhaps we can invite you up to give that answer.

DR. GINSBERG: Sure.

DR. GOLDFINE: And the final question will

be Dr. Spruill?

DR. SPRUILL: I want to go back to the question about gender, but I want to add ethnicity to it as well. I want to talk about the clarification of your design of the study. It seems as though you excluded the high-risk population. And if you excluded a high-risk population that clearly has the higher percentage of complications and death from diabetes, then how confident are you in your evidence that this will work for this particular high-risk population? Because when I looked at the study, I think you had less than 20 percent of ethnic minorities.

DR. SPRUILL: So the minorities, there were -- if you took African-Americans and blacks overall, I think that was 22 percent. There was another 8 percent other, and either non-defined or Asian or others, other-others, and then about 70 percent Caucasian.

The population chosen was very high risk for cardiovascular disease overall. In order to get into this trial, you had to have a duration of

diabetes of 10 years, I believe, it was. But you had to have CHD, or CVD, or pre-clinical evidence of CHD, such as a calcium score or a stress test that was positive, or you had to have at least two other risk factors besides diabetes. So you know these trials are always focused on the events. They need to prove the hypothesis. So it's a very high-risk population. And non-whites would have the same criteria to get in the trial.

It turned out that, for everybody, the actual event rates vary because we have some algorithms based on epidemiology that lump everybody together, and your overall event rate was just where we thought it would be, 2.4 percent per year, but obviously some people were half of that and some people were double that. And it turned out that the non-whites had lower event rates despite having similar inclusion criteria.

Why that's so? To me, my view of that is that the criteria that I just described to give high risk for events were not lipid criteria. And so there's no doubt that if you want to criticize

the trial, the criticism is based on not doing the trial on the dyslipidemic population. And as I said, this was not the trial designed primarily to do that.

In fact, if you go to look at the blood pressure arm of this trial, they also suffered from being a substudy in that people who met the lipid criteria went into our trial. People who didn't meet lipid criteria but had blood pressure criteria went into their trial, and they ended up with higher HDLs than expected, and lower triglycerides than expected, and lower event rates than they expected.

So I think we've learned a lesson here that I think we did have more bang for the buck by doing three trials in one, but there are shortcomings to all clinical trials. And in this case, one of the shortcomings was clustering the two, the blood pressure and the lipid trials, under the glycemic umbrella.

DR. GOLDFINE: Thank you very much.

I will now take a 10-minute break. Panel

members, please remember that there should be no discussion of the meeting topic during the break amongst yourself or with any member of the audience, and we will resume at 9:45 a.m.

(Whereupon, a recess was taken.)

MR. TRAN: Please take your seat. We will restart the meeting. Thank you.

DR. GOLDFINE: I'd like to reinvite Dr. Ginsberg up to the podium. There was a question for him on statistics that he didn't have the answer to before, that he can now address.

DR. GINSBERG: Tim Craven is one of the statisticians of the coordinating center, took a quick run through the Eye paper. And there is no information in there that allows me to answer definitively, but I'm assuming, therefore, that we did not make corrections for multiple comparisons. However, with a p value of .006, it's not going to go away with typical corrections. But it looks like, in the paper, the published data are not corrected.

DR. GOLDFINE: Thank you very much for that

clarification, and for your entire presentation, Dr. Ginsberg.

We'll now proceed with the sponsor presentations. I would like to remind the public observers at this meeting, that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual presentation.

For this reason, FDA encourages all participants, including the sponsors, non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based on the

outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationship. If you choose not to address this issue of financial relationship at the beginning of your presentation, it will not preclude you from speaking.

Sponsor Presentation – James Stolzenbach

DR. STOLZENBACH: Thank you very much.

My name is Jim Stolzenbach. I'm the R&D divisional vice-president for dyslipidemia at Abbott. And on behalf of Abbott, we appreciate the opportunity to meet with you today to discuss the implications of the ACCORD Lipid study results on the use of fibrate and statin coadministration therapy.

The ACCORD trial was not designed or conducted by Abbott and it was sponsored by the NHLBI. Following the release of the results from ACCORD, the NHLBI shared a portion of the database with Abbott so we could more completely understand

the results of the study. We'd like to emphasize that we did not receive the entire database, and, therefore, we may not be able to answer all of your questions and apologize in advance if there are some discussions that we cannot respond to because we don't have the data.

You heard from Dr. Ginsberg earlier this morning that the results of the ACCORD Lipid study did not demonstrate a significant cardiovascular risk reduction for the overall study population. In response to these trial findings, the FDA is reviewing the study results and how they relate to the Trilipix coadministration indication. As part of their review, the FDA has scheduled this advisory committee meeting.

Abbott is here at the request of the FDA so that we may all discuss the questions that the FDA has posed to the committee. Abbott is not seeking any additional indication, nor are we trying to expand the patient population indicated for coadministration therapy.

Abbott's presentation today will support our

assessment of the data. First, we'll show that the ACCORD Lipid results confirm results from other studies, that patients on statin monotherapy are still at significant risk for future cardiovascular events.

We'll then demonstrate that the data from ACCORD Lipid support the use of statin and fibrate coadministration therapy in a readily identified population of these high risk patients. We'll also place ACCORD Lipid in context with other fibrate outcomes trials and show the consistency of the results across these trials in patients with dyslipidemia.

Next, we'll show that the safety profile of fenofibrate and fenofibric acid is well defined, it's consistent with our labeling, and it's acceptable when administered with a statin.

Finally, we'll conclude that the total body of data shows a positive risk benefit profile for coadministration therapy and it supports the approved indication for Trilipix.

Our agenda today includes the following

components. Dr. Maureen Kelly, the Abbott project and medical leader responsible for Trilipix, will review the data from our Trilipix Phase 3 clinical development program. She will review additional analyses conducted by Abbott from ACCORD Lipid and other fibrate outcomes trials. Dr. Kelly will also discuss important safety considerations and the unique microvascular benefits of fenofibrate therapy.

Following Dr. Kelly, Dr. Peter Jones, from Baylor College of Medicine, will provide a clinician's perspective on the use of fibrate therapy in combination with statins, and then I'll summarize with a few brief conclusions.

In addition to Dr. Jones, we have four experts with us today to help contribute to the discussion. These experts are Professor Anthony Keech, the principal investigator from the FIELD trial; Professor Gary Koch from the University of North Carolina; Dr. Cheryl Enger, an epidemiologist from Innovus; and Dr. Jaap Mandema, a meta-analysis consultant from Quantitative Solutions.

Treatment with fibrates as monotherapy has a long history, and the fibrates listed here comprise the clinical class. Only three fibrates are available in the United States. Gemfibrozil is not recommended for combination therapy with statins, due to unfavorable pharmacokinetic interactions leading to higher rates of rhabdomyolosis, and, therefore, it's not the focus of the discussion today.

Fenofibrate was the fibrate that was used in ACCORD Lipid, and as a prodrug for the active moiety fenofibric acid. Trilipix is the choline salt of fenofibric acid, so both fenofibrate and Trilipix share the same active moiety. Trilipix is the only fibrate in the U.S. with a coadministration indication with statins.

Now, the fibrates activate a nuclear PPAR-alpha receptor that results in the reduction of triglyceride levels and increase in HDL. This mechanism is separate from that of the statins and is the basis for the rationale that adding a statin to a fibrate, or adding a fibrate to a statin, will

cause additional decreases in triglycerides and increases in HDL.

There have been two fibrate outcomes trials that have been conducted with fenofibrate, ACCORD Lipid, which Dr. Ginsberg has reviewed for us this morning, and FIELD, which was an investigator-initiated study supported by Fournier Pharmaceuticals, which is now a part of Abbott.

FIELD was conducted outside of the U.S. as a trial of fenofibrate monotherapy versus placebo in type 2 diabetic patients. The FIELD trial was approximately twice the size of ACCORD Lipid and included 37 percent women. Like ACCORD Lipid, the majority of the patients in FIELD had only a modest degree of dyslipidemia. Although the FIELD results did not reach statistical significance for the primary endpoint of coronary outcomes, the pre-specified secondary endpoint, which included a broader definition of cardiovascular events, was positive in favor of fenofibrate.

ACCORD Lipid is the only cardiovascular outcomes trial evaluating fenofibrate in

combination with a statin. Neither FIELD nor ACCORD Lipid were designed to answer the question of whether or not a combination of a statin would reduce cardiovascular events in patients with elevated triglycerides and/or low HDL. Rather, the studies were designed to determine if fenofibrate reduced cardiovascular risk in a broader group of diabetic patients with only modest abnormalities and baseline lipids.

So Abbott has, therefore, worked closely with the NHLBI and the FIELD investigators to obtain data from these studies that's pertinent to today's discussion, and we'd like to thank Professor Keech and Dr. Ginsberg, as well as the steering committees, for their willingness to work with us.

The chronology of fenofibrate and Trilipix development, along with the timing of the results from the FIELD and ACCORD Lipid studies, provide important context for the discussions today. Fenofibrate was approved in France in 1975 and approvals in other countries followed France. In

the U.S., fenofibrate was first marketed in 1998.

In the lower half of the slide, it's shown that the ACCORD trial was started in January of 2001. This is well in advance of the availability of the FIELD results that were disclosed at the end of 2005. Therefore, the FIELD results did not inform the ACCORD investigators on the design of the ACCORD Lipid trial.

Trilipix was approved in the United States in December of 2008 with an indication for coadministration therapy with statins. This was based on an Abbott-conducted Phase 3 program including approximately 2700 patients with high triglycerides and low HDL.

We'll focus on the statin coadministration indication for this meeting, but as Dr. Colman has already indicated, Trilipix also carries the same monotherapy indications as fenofibrate. The coadministration indication reads as follows. Trilipix is indicated as an adjunct to diet, in combination with a statin, to reduce triglycerides and increase HDL in patients with mixed

dyslipidemia and coronary heart disease, or a coronary heart disease risk equivalent, who are on optimal statin therapy to obtain LDL control.

The ACCORD Lipid results were released in March of 2010. And soon thereafter, the FDA announced that they would review the Trilipix label for coadministration therapy. Abbott then contacted the NHLBI to obtain additional data from this study, allowing us to better understand the findings.

We held a meeting with the FDA in June of 2010. The Abbott analyses from the ACCORD Lipid database and other data were presented at that meeting. When the meeting was concluded, the FDA determined that there was no immediate change to the prescribing information required, but the agency did indicate that further discussions would be conducted and that a future advisory committee meeting was a possibility.

Outside of the U.S., Abbott provided the ACCORD Lipid results in our additional analyses to the European regulatory agency, the CHMP, in light

of the FIELD and ACCORD Lipid data. Within the U.S., the FDA scheduled this advisory committee meeting.

In October of 2010, when Abbott met with the CHMP, the topic was to discuss the European prescribing information for fenofibrate. Based on the data from ACCORD Lipid, as well as other data, the CHMP revised the fenofibrate indication to allow for coadministration with a statin in a population of patients that are appropriate for combination therapy. This is consistent with the current U.S. labeling for Trilipix.

This brings us to today this committee meeting. To support the meetings that we've had with regulators and with our discussion today, Abbott has analyzed the data from ACCORD Lipid and also reviewed the data from multiple information sources. This includes data from other fibrate and statin cardiovascular outcome trials with meta-analyses conducted by Abbott, as well as independent investigators.

We have reviewed data from the Trilipix

development program and our postmarketing safety, and prescription use data. The review of all these data, which we'll summarize for you today, has led Abbott to conclude that the totality of data supports the coadministration therapy claim in appropriate patients and that these patients are readily identifiable. ACCORD Lipid, in particular, supports the coadministration therapy indication where it's clear that risk remains even after LDL targets are reached on statin monotherapy.

Analyses of the fibrate outcome studies, including ACCORD Lipid, have consistently demonstrated that cardiovascular risk reduction is evident in patients with abnormal triglycerides and low HDL. The safety profile of fenofibrate and fenofibric acid is well understood, and it's consistent with our current prescribing information. Based on all of these data, Abbott concludes that there is ample evidence supporting the coadministration indication for Trilipix.

This concludes my overview, so please let me now introduce the Abbott Trilipix project leader,

Dr. Maureen Kelly.

Sponsor Presentation – Maureen Kelly

DR. KELLY: Good morning. My name is Maureen Kelly, and I am Abbott clinical lead for Trilipix. This morning, we will review data from the Trilipix clinical program, discuss previous fibrate outcomes trials, and go through additional analyses of ACCORD Lipid. We will also examine data from other sources that support coadministration therapy. Finally, we will present the safety profile of coadministration therapy.

The Trilipix clinical program that led to approval in 2008 comprised four studies. Three were 12-weeks lipid efficacy studies that evaluated coadministration therapy with Trilipix and a statin. The fourth was a long-term open label study that evaluated Trilipix, coadministered with a statin, that enrolled subjects from all three of the lipid efficacy studies.

The Trilipix clinical program was the first to evaluate a fibrate coadministered with three different statins. The program enrolled nearly

2700 patients at 500 investigative sites in Canada and the United States, including Puerto Rico. The program was designed to evaluate patients with mixed dyslipidemia and therefore required patients to meet LDL, triglyceride, and HDL entry criteria after washout of lipid-altering drug therapy. The baseline lipid values of the enrolled population following washout demonstrate the presence of mixed dyslipidemia.

This figure depicts the design of the studies in the Trilipix clinical program. The three double-blind controlled studies randomized patients to one of six treatments, low-, moderate-, or high-dose statin monotherapy, Trilipix coadministered with low- or moderate-dose statin, or Trilipix monotherapy.

Each of the three studies evaluated a different statin: rosuvastatin, simvastatin, or atorvastatin. These represent the three most commonly prescribed statins in the United States. The specific statin doses studied with Trilipix were 10 and 20 milligrams for rosuvastatin, and 20

and 40 milligrams for atorvastatin and simvastatin. Patients completing each of the three controlled studies were allowed to enroll in a one-year open label extension study where they received moderate-dose statin, coadministered with Trilipix.

All three double-blind controlled studies met their primary endpoint, a composite of LDL, HDL, and triglycerides. Today, we will review the results for the simvastatin study, as this was the statin used in ACCORD Lipid. Results were generally similar for the other two studies that evaluated rosuvastatin and atorvastatin.

Statin monotherapy arms are shown at the top of the figure in green, and Trilipix-containing arms are shown at the bottom of the figure in blue. There are two findings to highlight from this study. First, that Trilipix-containing arms provided significantly greater improvements in triglycerides, shown on the left of the figure, and significantly greater improvements in HDL, shown on the right of the figure, then statin monotherapy; and second, that in the statin monotherapy arms,

there was no clear dose-response relationship, that is, higher simvastatin doses did not provide better triglyceride and HDL improvements than lower doses.

Several outcome studies provide important information about the cardiovascular benefits of fibrates. The Helsinki Heart Study, HHS, the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial, VA-HIT, the Bezafibrate Infarction Prevention study, BIP, and the Fenofibrate Intervention and Event-Lowering in Diabetes trial, FIELD, are the four key fibrate trials that reported results before ACCORD Lipid. All were studies of fibrate monotherapy versus placebo.

Design features varied among these four studies, including the fibrate studied, the sample size, and the patient population. Each of these four trials showed a reduction in the pre-specified primary cardiovascular endpoint.

On the surface, it might appear that the cardiovascular benefit of fibrate monotherapy was not consistent across these trials because the

improvement was significant for only two of the trials. However, when we look more closely, each of these trials actually tells the same story.

For each trial, results were published for a subgroup of patients with elevated triglycerides and low HDL at baseline. In each study, patients with elevated triglycerides and low HDL treated with a fibrate demonstrated a significant reduction in cardiovascular risk. The criteria for defining each subgroup were similar across the trials, with the triglyceride cutoffs ranging from 180 to 204, and the HDL cutoff ranging from 35 to 42.

The combined analysis across all four trials in these patients demonstrated an odds ratio of .62, corresponding to a 38 percent reduction in the odds of a cardiovascular event with fibrate therapy.

Just as important, when we look at the remaining patients, those without both elevated triglycerides and low HDL, referred to here as all others and shown on the right, we again see consistent results across the trials.

None of the trials individually demonstrated a significant reduction in cardiovascular events for these patients. The combined analysis across all four trials in these non-dyslipidemia patients demonstrated an odds ratio of .91, corresponding to a 9 percent reduction in the odds of a cardiovascular event, which was not statistically better than placebo.

So prior to the presentation of the results of ACCORD Lipid, data from these four key fibrate outcomes trials supported two equally important hypotheses. The data demonstrated first that fibrates reduced the risk of cardiovascular events in patients with elevated triglycerides and low HDL, and second, that fibrates do not provide a meaningful reduction in cardiovascular risk in non-dyslipidemia patients.

Dr. Ginsberg spoke about the design of ACCORD Lipid earlier this morning. Here, we highlight two of the study's design features. First, there was no minimum threshold for triglycerides at study entry, leading to an

enrolled population where only a subset of patients demonstrated hypertriglyceridemia. Second, at the time of enrollment, some patients were receiving a statin and some were not, which means the baseline lipid values in the study are a mix of treated and untreated values.

On the next several slides, I'm going to review the results for the pre-specified subgroup with dyslipidemia. As you saw in Dr. Ginsberg's presentation, this group is made up of 941 patients with baseline triglycerides in the highest tertile, 204 or more, and baseline HDL in the lowest tertile, 34 or less.

The primary outcome for the overall ACCORD Lipid study is shown in the top row. In the blue box are the results for the pre-specified subgroup with dyslipidemia compared to all others. The p value for the treatment by subgroup interaction was 0.057. In the pre-specified subgroup, there was a reduction in cardiovascular risk with a nominal p value of 0.032. In all others, there was no difference between treatment groups in the

primary outcome.

In patients in the pre-specified subgroup with dyslipidemia, receiving coadministration therapy with fenofibrate and simvastatin, 12.4 percent experienced a primary event compared with 17.3 percent in the subgroup with dyslipidemia, receiving simvastatin monotherapy. This cardiovascular risk reduction translates to a number needed to treat, or NNT, of 20 patients for an average of 4.7 years to prevent one primary endpoint event.

Again, similar to other fibrate trials, there was no statistically significant cardiovascular benefit demonstrated in the all-others group, that is, patients not meeting the pre-specified dyslipidemia definition.

This figure shows the Kaplan-Meier plot for the patients in the pre-specified subgroup with dyslipidemia. The lines give the proportion of patients with the primary endpoint over time, and they illustrate the reduced risk for a primary endpoint in the coadministration group. The hazard

ratio for the comparison of the treatment groups was .69, corresponding to a 31 percent reduction in risk.

The benefit of coadministration therapy in the pre-specified subgroup with dyslipidemia was not limited to the primary endpoint. On the top half of the slide are the results for the pre-specified subgroup with dyslipidemia, and on the bottom half of the slide are the results for the all-others group. Coadministration therapy reduced the risk of pre-specified secondary endpoints, including the two composite endpoints, the expanded macrovascular endpoint, and the major coronary disease endpoint.

Additionally, coadministration therapy reduced the risk of cardiovascular disease mortality. The consistency of the effect of coadministration therapy for the pre-specified subgroup with dyslipidemia across these endpoints supports the presence of a biologic effect of fenofibrate therapy in this group.

If we return to the primary endpoint, we can

put the results of ACCORD Lipid in the context of the previous fibrate trials. When we do that, we see that the results are entirely consistent, both for the patients with elevated triglycerides and low HDL, and for all others; that is, those without elevated triglycerides and low HDL.

In patients with elevated triglycerides and low HDL, the results of ACCORD Lipid were similar to those of the other studies. And based on all five studies, the odds ratio for patients treated with a fibrate was 0.65, corresponding to a 35 percent reduction in the odds of a cardiovascular event. In the all-others group, ACCORD Lipid was also consistent with prior studies. When all five studies are combined, the odds ratio was 0.93, corresponding to a 7 percent reduction in a cardiovascular event, which did not achieve statistical significance.

The previous trials illustrated that fibrate monotherapy provides cardiovascular benefit in patients with high triglycerides and low HDL. And ACCORD Lipid illustrated that cardiovascular

benefit is also present when fenofibrate is coadministered with a statin in this population.

In contrast, for both fibrate monotherapy and fenofibrate statin coadministration therapy in patients without elevated triglycerides and low HDL, there is no evidence of a meaningful cardiovascular risk reduction, which is attributable to the modest degree of dyslipidemia present.

Another design feature of ACCORD Lipid is that there was a one-month simvastatin monotherapy phase prior to initiation of blinded fenofibrate or placebo. Lipid values were not assessed after the simvastatin monotherapy phase. Therefore, the only lipid values prior to blinded drug therapy in ACCORD Lipid were those obtained at study entry. These represent statin-treated values for 60 percent of enrolled patients and untreated values for 40 percent of enrolled patients. This means, for 40 percent of patients not on statin at baseline, we do not know if statin monotherapy was all that they needed; that is, there's no way to

know if these patients would be candidates for coadministration therapy after statin monotherapy. When we look at the impact of baseline lipid values on cardiovascular benefit, the most appropriate population to examine are those patients who were receiving a statin at baseline.

So we have looked at the pre-specified subgroup with dyslipidemia, and we have seen that there is a reduction in cardiovascular risk with coadministration therapy. Next, we conducted two sensitivity analyses to help us assess the robustness of these findings.

For the first sensitivity analysis, we are going to divide the pre-specified subgroup with dyslipidemia into those patients who are receiving a statin at baseline, 477 patients, and those who were not receiving a statin at baseline, 464 patients.

The rationale for looking at results by whether patients were at baseline receiving a statin is based in part on the Trilipix prescribing information, which states that patients should be

receiving a statin prior to the addition of Trilipix. This is in line with treatment guidelines, which specify that coadministration therapy should be considered only if abnormalities of triglycerides and HDL persist after statin treatment.

At the top of the figure are the results for the pre-specified subgroup with dyslipidemia that you've seen earlier. In the blue box, that group is divided into patients who were receiving a statin at baseline and patients who were not. These results tell us that within the pre-specified subgroup with dyslipidemia, the reduction in cardiovascular risk is driven by the patients who were receiving a statin at baseline. In that group, the hazard ratio is 0.55 with a nominal p value of 0.01. In the patients not receiving a statin at baseline, in contrast, the hazard ratio was near 1.

If we look at the proportion of patients with the primary endpoint in the simvastatin monotherapy arm, we get insight into why this is

happening. In patients receiving a statin at baseline, the event rate is over 21 percent, but in patients not receiving a statin at baseline, it's only 13 percent.

What this highlights is that statin-treated lipid values mean something quite different than untreated lipid values. Patients who were receiving a statin at baseline and still had triglyceride values of at least 204 and HDL of 34 or less were at much greater risk on statin monotherapy than patients whose untreated lipid values met these criteria. This makes perfect sense. Many of the untreated patients who met the criteria for the subgroup with dyslipidemia would not have met the criteria if they had been receiving a statin.

So the first sensitivity analysis illustrated that the cardiovascular benefit of coadministration therapy in the pre-specified subgroup with dyslipidemia is primarily driven by those subjects who had elevated triglycerides and low HDL despite receiving statin therapy.

The question that arises is whether coadministration therapy reduces cardiovascular risk in a population that is based on thresholds of triglycerides HDL and identified by NCEP treatment guidelines, as opposed to the tertile thresholds of ACCORD Lipid.

The NCEP treatment guidelines identify triglycerides above 200 for consideration of additional therapy beyond statin treatment, with non-HDL as the target of therapy. Further, the guidelines identify HDL values below 40 as categorically low and suggest that high-risk patients with elevated triglycerides or low HDL can be considered for additional therapy beyond a statin.

Let me take a minute to put the various thresholds into context. This box represents all patients in ACCORD Lipid who are receiving a statin at baseline. We are going to look at them by baseline triglyceride levels, reflected on the vertical axis, and baseline HDL levels, reflected on the horizontal axis. The yellow box represents

patients who were receiving a statin at baseline and were in the pre-specified subgroup with dyslipidemia; that is, they had triglycerides of at least 204 and an HDL less than 34.

Here, we see the triglyceride and HDL thresholds described in the treatment guidelines, shown as dashed lines to represent a triglyceride cutoff of 200 and an HDL cutoff of 40.

So the broader population that might be considered for coadministration therapy is shown here in blue, and you can see how it differs from the pre-specified subgroup with dyslipidemia. The question, then, is whether coadministration reduces cardiovascular risk in the patients represented by the area in blue. So the second sensitivity analysis that we conducted is of this group in blue.

On the top row of this forest plot, it shows the patients in the blue area on the prior slide; that is those patients who were receiving a statin at baseline and had triglycerides of 200 or more, HDL less than 40, or both. The hazard ratio was

0.76, with a nominal p value of 0.021, and the p value for the treatment by subgroup interaction was 0.024. This second sensitivity analysis therefore shows that coadministration therapy reduced cardiovascular risk in this population that might be considered appropriate for coadministration therapy according to treatment guidelines based on their on-statin triglycerides and HDL.

The point of this analysis is not to establish definitive thresholds for coadministration therapy, but to demonstrate that the benefit of coadministration therapy is present beyond the limits of the pre-specified subgroup with dyslipidemia. We have looked at the hazard ratios in these different sensitivity analyses, but to put these analyses into context, let's look at the individual treatment arms and the event rates that went into the calculation of these hazard ratios.

This figure represents patients in the simvastatin monotherapy arm receiving a statin at

baseline. The bar on the left represents all patients in this arm who were receiving a statin at baseline with any baseline HDL level or triglyceride level. Thirteen percent of these patients had the primary endpoint during the study. The bar in the middle shows that the event rate is 15 percent in patients with baseline HDL below 40.

The event rate goes up to 19 percent in the right-hand bar, representing patients with HDL less than or equal to 34. Patients with the lowest baseline HDL were at highest risk for a primary outcome.

Next, we look at the same analysis but focus on patients with higher triglycerides of 200 or more. For example, when we look at patients who had baseline HDL of 34 or less, the event rate was 19 percent, but when we look at just those with higher baseline triglycerides of 200 or more, the event rate increased to 21 percent. There was a similar relationship for the other HDL levels.

Finally, for completeness, the event rates based on the triglyceride threshold of 204 are

shown here. Of course, since this threshold is so close to the threshold of 200 used for the middle row, the event rates are very similar.

The overall message from this figure is that as baseline triglycerides increase and HDL decreases, the risk of a cardiovascular event goes up. Therefore, ACCORD Lipid results are completely in line with the epidemiological data for triglycerides and HDL. Patients on statins to control their LDL, have residual risk, and that risk is related to their on-statin triglyceride and HDL levels.

Now, let me show you the same plot for the coadministration arm. In striking contrast, in the coadministration arm, the cardiovascular event rates were lower and relatively uniform across the various HDL and triglyceride cutoffs. Thus, the excess risk associated with elevated triglycerides and low HDL in the simvastatin monotherapy arm was mitigated with the addition of fenofibrate.

Because treatment guidelines identify non-HDL as the secondary target of therapy, we

conducted an analysis using non-HDL. We evaluated patients in ACCORD Lipid receiving a statin at baseline who had controlled LDL, less than 100, but uncontrolled non-HDL, greater than 130. Event rates were 8.8 percent for the coadministration arm and 16.3 percent for the simvastatin monotherapy arm. The hazard ratio was 0.51 and the nominal p value was 0.023. This analysis further reinforces the benefit of coadministration therapy in this guidelines-based analysis.

In ACCORD Lipid, in patients with elevated triglycerides and low HDL, coadministration therapy conferred a greater reduction in cardiovascular events than simvastatin monotherapy. The benefit observed in this group was concentrated in patients who were receiving a statin at baseline and still met dyslipidemic criteria.

The results of ACCORD Lipid are consistent with the known relationship between triglycerides and HDL, with event rates increasing with more severe dyslipidemia for patients receiving simvastatin monotherapy.

The second focus of our analyses was an evaluation of the effect in women in ACCORD Lipid. In the overall ACCORD Lipid population, a treatment by gender interaction was observed, suggesting the potential for a less favorable benefit risk profile of coadministration therapy in women.

To further investigate this observation, we assessed outcomes in women with dyslipidemia and looked at possible explanations for this finding. In the pre-specified subgroup with dyslipidemia, there was no treatment by gender interaction. This means that we do not have a reason to believe that the benefit of coadministration therapy observed in this group varied by gender.

This next analysis corresponds to the first sensitivity analysis; that is patients who were in the pre-specified subgroup with dyslipidemia and receiving a statin at baseline. Likewise, there was no treatment by gender interaction in this group.

Finally, this analysis represents the second sensitivity analysis; that is patients who were

receiving a statin at baseline and had either triglycerides of 200 or more, HDL less than 40, or both. Again, there was no significant treatment by gender interaction observed in this group.

These are the event rate figures for men, and the relationship is very similar to the overall figures. That is, for men in the simvastatin monotherapy arm, the risk of a primary outcome increased as the triglycerides increased and as HDL decreased. In the coadministration arm, the event rates were generally flat, suggesting that the addition of fenofibrate mitigated the excess risk associated with triglyceride and HDL abnormalities.

Here are the event rate figures for women, and we see a similar relationship. In the simvastatin monotherapy arm, event rates increased with increasing triglycerides and decreasing HDL. But in the coadministration arm, the event rates are relatively flat, regardless of baseline triglycerides and HDL. While the sample sizes are small in some of these groups, the pattern is very similar to the pattern in men, suggesting that the

same biologic effects are present in men and women.

In order to assess potential explanations for the findings in the overall ACCORD Lipid population in women, Abbott evaluated the possible causes for the observation. First, pharmacokinetic interaction data for fenofibrate and statins was reviewed. There was no difference between men and women identified. Abbott also reviewed available clinical data, and no prior study was identified with a similar treatment by gender interaction. Within ACCORD Lipid, no baseline imbalances were found. Multivariate analysis did not result in meaningful changes to the treatment effect in women. Lipid changes were not substantially different between men and women.

Abbott's investigation of possible etiologies for the treatment by gender interaction in ACCORD Lipid yielded no identified cause. This interaction is unsubstantiated by data from other studies, including FIELD. The treatment by gender interaction is not present in the pre-specified subgroup with dyslipidemia. In contrast, the

treatment by dyslipidemia subgroup interaction in ACCORD Lipid is both consistent with the known mechanism of action and lipid effects of fenofibrate and has been observed in prior fibrate trials.

The safety profile for fenofibrate statin therapy in ACCORD Lipid was reassuring. Study drug discontinuations and laboratory abnormalities of interest, such as elevations in creatinine kinase and ALT, occurred at expected or lower frequencies in ACCORD Lipid. There was no significant difference in reports of hepatitis or pancreatitis between treatment arms, and coadministration was not associated with a greater risk of important renal outcomes, including hemodialysis and diagnosis of end-stage renal disease.

Examination of additional information from non-ACCORD sources also supports the use of coadministration therapy. Data presented will include meta-analyses and a review of the microvascular benefits of fenofibrate therapy.

Abbott conducted a meta-analysis of 71

outcome trials with cardiovascular and/or coronary outcomes, including over 215,000 patients. These included primarily statin trials but also seven fibrate trials. This meta-analysis evaluated the correlation between lipid parameters, including LDL, triglycerides, and HDL, and cardiovascular and coronary outcomes. In addition to treatment duration and baseline HDL, the magnitude of decrease in LDL and triglycerides were independent and additive contributors to decreases in cardiovascular risk.

Based on the observed differences between treatment arms in ACCORD Lipid for triglycerides, and accounting for the fact that there was very little difference in LDL between treatment arms, the Abbott meta-analysis model predicts a hazard ratio of 0.90 for cardiovascular outcomes and 0.91 for coronary outcomes. These are nearly identical to the 0.92 hazard ratio observed in the overall population in ACCORD Lipid.

The Abbott meta-analysis accurately predicts not just the results of ACCORD Lipid, but each of

the key fibrate outcomes trials. The blue square and the vertical hash mark represent the observed and predicted hazard ratio for each of these studies.

An independent fibrate meta-analysis published in Lancet, evaluating 18 fibrate trials, including ACCORD Lipid, included over 45,000 patients. This analysis identified a 10 percent reduction in major cardiovascular disease events and a 13 percent reduction in coronary events with fibrate therapy. As expected, a larger effect was noted in trials with higher baseline triglycerides and larger absolute triglyceride differences.

In this meta-analysis, non-fatal coronary events were the main contributor to the benefits seen with fibrates. In the meta-analysis, fibrates were associated with a lower rate of progression of albuminuria. This, and other microvascular benefits, have been demonstrated with fenofibrate in patients with diabetes.

These microvascular benefits of fenofibrate include reduction in the progression of retinopathy

and also the need for laser treatment for retinopathy. Retinopathy benefits of fenofibrate were observed in pre-specified substudies in ACCORD Lipid and FIELD. Also observed in both FIELD and ACCORD Lipid was a reduction in the progression of albuminuria and the incidence of micro- and macroalbuminuria.

In FIELD, a benefit of fenofibrate therapy was observed on the development of new neuropathy, as well as a reduction in pre-existing neuropathy. Fewer total amputations were observed in fenofibrate-treated patients.

To further understand the safety of fenofibrate and fenofibric acid, we reviewed several sources of safety data, including clinical trial data, epidemiology data, and postmarketing safety data. To evaluate the safety, we will review the current clinical utilization of fenofibrate and fenofibric acid and discuss specific safety events known to be associated with fibrate use.

Abbott has conducted analyses to understand

how dyslipidemic patients are currently being treated with fenofibrate and fenofibric acid in clinical practice. The GE Centricity database was utilized to understand prescribing patterns for fenofibrate and fenofibric acid. It represents a large number of patients, including 2.3 million patients with dyslipidemia. This database provided access to electronic records, including laboratory and prescription data.

This analysis identified over 13,000 patients receiving a statin who initiated fenofibrate or fenofibric acid therapy. Triglyceride levels at the time of fenofibrate or fenofibric acid initiation for the overall group, as well as for men and women separately, showed mean and median values near or above 300 for triglycerides. For HDL, the overall value for those initiating fenofibrate or fenofibric acid, in addition to a statin, was 38, with women demonstrating higher values than men.

The vast majority of patients in this real-world usage analysis had triglyceride values above

200 and/or HDL values below 40 at the time of initiation of fenofibrate or fenofibric acid. Therefore, the current usage of coadministration therapy is within clinically appropriate parameters and also in alignment with the approved Trilipix coadministration indication.

One important safety consideration with lipid drug therapy is rhabdomyolysis. There are three large observational database studies that have evaluated hospitalized rhabdomyolysis associated with statin and/or fibrate therapy. Two have been published in peer-reviewed journals, the analysis by Dr. David Graham and i3/Abbott Study 1.

The most recent study, i3/Abbott Study 2, was sponsored by Abbott and conducted in collaboration with i3, a large health economics and outcomes research company, as part of a post-approval commitment for Trilipix. This study was the largest of the three, with 70 cases of rhabdomyolysis. Dr. Graham's analysis included 24 cases and i3/Abbott Study 1 included 22 cases of hospitalized rhabdomyolysis.

The larger number of events in i3/Abbott Study 2 is due to the larger sample size and larger number of patient years of follow-up. Each of these studies evaluated events coincident with the use of lipid-lowering drugs as monotherapy or as coadministration.

This slide shows the overall incidence rates for hospitalized rhabdomyolysis from the three observational studies in patients receiving either statin monotherapy, fibrate monotherapy, or coadministration therapy. Neither of the i3/Abbott studies capture events for cerivastatin, a product withdrawn from the U.S. market in 2001. Therefore, we also calculated incidence rates for Dr. Graham's analysis with cerivastatin cases removed.

The overall incidence rates for rhabdomyolysis are generally similar in all three studies. As FDA noted in their briefing book for today's meeting, there were modest differences in the case definition between the studies that may have accounted for the lower rate in the i3/Abbott studies.

Consistently across the two i3/Abbott observational studies, an increased relative risk for hospitalized rhabdomyolysis was observed with coadministration therapy compared to statin monotherapy. However, the event of hospitalized rhabdomyolysis is rare. A number needed to harm was calculated from the i3/Abbott studies for statin fenofibrate coadministration therapy. Beyond statin monotherapy, one would need to treat 11,000 to 18,000 patients for one year with fenofibrate statin coadministration therapy to observe one additional rhabdomyolysis case.

The FDA described an NNH in their briefing book of 6,700. This calculation may be somewhat smaller because it is based on crude-rate differences and included events for gemfibrozil and fenofibrate when coadministered with a statin.

Rhabdomyolysis during lipid-altering drug therapy is rare. In ACCORD Lipid, no significant increase in the rate of muscle events was observed in the patients receiving coadministration therapy compared to simvastatin monotherapy. Observational

pharmacoepidemiological studies are the best way to review rare events such as hospitalized rhabdomyolysis.

i3/Abbott Study 2 of hospitalized rhabdomyolysis is the largest such study ever conducted. A modest increased risk of hospitalized rhabdomyolysis was detected for patients receiving coadministration therapy with fenofibrate and a statin, compared to statin monotherapy. However, the number needed to harm for the event is very large.

The data available for the event of hospitalized rhabdomyolysis support that the discussion of rhabdomyolysis in the approved prescribing information for Trilipix, which includes a patient medication guide, is appropriate.

Renal events, pancreatitis, and hepatic events are associated with the use of fenofibrate and have been evaluated further. We evaluated not only the results of the i3/Abbott Study 1, but also available clinical trial safety data for these

three events. Each of these events are currently included in the warnings and precautions section of the Trilipix prescribing information.

Renal safety was evaluated utilizing data from ACCORD Lipid, FIELD, and i3/Abbott Study 1. In both ACCORD Lipid and FIELD, reversible increases in creatinine were observed. These creatinine increases were not associated with an increased rate of important renal outcomes such as diagnosis of end-stage renal disease or need for hemodialysis. In fact, in both ACCORD Lipid and FIELD, patients receiving fenofibrate had numerically fewer of these outcomes.

i3/Abbott Study 1 found a 1.5-fold increased risk for renal impairment as defined by an increase in creatinine for fenofibrate statin coadministration patients, compared to patients receiving statin monotherapy. These findings are, again, consistent with the well-described reversible increases in creatinine in patients receiving fenofibrate therapy.

Data from the FIELD renal substudy are

provided on this slide. In 661 FIELD participants, who were followed with an additional creatinine determination eight weeks after discontinuation of study medication, creatinine was significantly lower in patients who had received fenofibrate than in those who had received placebo.

ACCORD Lipid and FIELD both demonstrated low rates of reporting events of pancreatitis. i3/Abbott Study 1 confirmed that the risk for pancreatitis, with fenofibrate monotherapy, is higher than with statin monotherapy, but did not demonstrate an increased incremental risk for fenofibrate statin coadministration therapy above fenofibrate monotherapy.

Similarly, ACCORD Lipid and FIELD provided consistent and reassuring data concerning hepatic safety. Transaminase elevations were observed with coadministration therapy or fenofibrate monotherapy at a low rate in ACCORD Lipid and FIELD. i3/Abbott Study 1 demonstrated no evidence for a differential risk for hepatic events between any exposure groups; that is, statin monotherapy or fenofibrate

statin coadministration therapy.

There have been over 35 years of safety experience with fenofibrate and fenofibric acid. A consistent and reassuring safety profile was observed in both ACCORD Lipid and FIELD. Specifically, recognized safety events and laboratory abnormalities such as renal events, pancreatitis, and hepatic events were noted to occur at a low rate and generally demonstrate reversibility. Observational data support these findings.

Additionally, for the event of hospitalized rhabdomyolysis, observational studies have demonstrated an event rate that is higher with fenofibrate statin coadministration therapy compared to statin monotherapy. However, the absolute incidence rates for hospitalized rhabdomyolysis is very low and the number needed to harm for statin fenofibrate coadministration therapy is very large.

ACCORD Lipid demonstrated that coadministration therapy reduces cardiovascular

risk in patients with elevated triglycerides and/or low HDL, as seen in the pre-specified subgroup with dyslipidemia and sensitivity analyses. There was no treatment by gender interaction in the pre-specified subgroup with dyslipidemia. Prescription usage data demonstrate that patients who have fenofibrate or fenofibric acid added to their existing statin therapy have elevated triglycerides and/or low HDL, consistent with the population demonstrated to derive benefit in ACCORD Lipid.

Additionally, fenofibrate has been demonstrated in ACCORD Lipid and FIELD to confirm microvascular benefits on patients with diabetes. The safety profile of fenofibrate and fenofibric acid is well-characterized, and the risks are appropriately described in the prescribing information.

I'm very pleased to introduce Dr. Peter Jones of Baylor College of Medicine in Houston, Texas, who will present a clinician's perspective on fenofibrate, fenofibric acid, and coadministration therapy in light of ACCORD Lipid.

Sponsor Presentation – Peter Jones

DR. JONES: Good morning. My name is Peter H. Jones. I'm an associate professor at Baylor College of Medicine, and I've been the founder and director of the Lipid Metabolism and Atherosclerosis Clinic there for the past 30 years. Abbott has paid me to be a past investigator, as well as an advisor, and my travel and attendance here today has been compensated. But my motivation for being here is to support continuing efforts to assertively identify, as well as appropriately treat, dyslipidemia in the clinical setting.

So I'm going to start with something you probably all know, that cardiovascular disease is the number one cause of death in the United States, and this is true for both men as well as women. In fact, cardiovascular disease accounts for at least 36 percent of all deaths in the United States.

Dyslipidemia is a major risk factor for cardiovascular disease, and is also very common in the United States. NHANES data estimates that approximately 100 million people in the U.S. have

dyslipidemia. Of those 100 million, about 60 million of them have elevated levels of LDL cholesterol. What's even more interesting is that a very similar number of those people, approximately 55 million, have low levels of HDL cholesterol, and approximately 28 million have high levels of triglycerides.

However, LDL cholesterol is the primary target of cardiovascular risk reduction for patients with dyslipidemia. And that is because there has been a consistent, log-linear relationship between LDL cholesterol and cardiovascular risk that's been well-established.

Now, this is a meta-analysis of 14 statin trials that included over 90,000 patients that was published in 2005. The meta-analysis demonstrated a relative risk reduction of 23 percent in major adverse cardiovascular events for a 1 millimole per liter reduction, LDL cholesterol, in statin-treated patients. This relationship was further confirmed and strengthened in a 2010 updated analysis that included 170,000 patients.

While statin treatment results are well-characterized and valued, we cannot allow ourselves to overlook the rest of the story in that these meta-analysis results would mean that a substantial residual cardiovascular risk of at least 65 to 75 percent remains, despite statin treatment.

Now, here, I've got a couple of landmark statin versus placebo trials that have been conducted over the last 20 years. The gray bars represent the placebo group and the blue bars represent the statin groups. The Y axis represents the cardiovascular event rate, and I think you can see overall there's a consistent pattern. Treatment with statins significantly reduces the relative risk for cardiovascular events, but it does not eliminate that risk.

Here, I have three more statin trials recently done that look at intensive versus moderate statin therapy. The light blue bars represent the standard statin therapy group and the dark blue bars represent the intensive statin therapy group. And the Y axis represents the

cardiovascular event rate. And even with intensive statin therapy, and this is maximal dose. a significant percentage of cardiovascular events still occur in these patients.

So what this tells us is that a significant residual risk remains even after maximal intensive statin therapy. So I guess the logical question to ask is, where does this residual risk come from if LDL cholesterol has been effectively managed by statins? It's possible that HDL might provide part of that answer.

So this slide displays the epidemiologic data from the Framingham Heart Study. At any level of LDL cholesterol, whether it be high, moderate, intermediate, or low, higher levels of HDL cholesterol are associated with lower risk for cardiovascular disease. But the question is, would lower levels of HDL cholesterol be associated with higher cardiovascular risk if LDL cholesterol, overall, was very well controlled? That's not what an epidemiologic study can tell us.

So this is an example of that, and this is

from the Treating to New Targets, or TNT study. Now, this study looked at intensive versus standard statin therapy in 10,000 patients with established stable coronary heart disease. The Y axis represents the cardiovascular event rate. The X axis represents the HDL levels by quintiles. This analysis includes only patients with an on-treatment LDL cholesterol level less than 70 milligrams per deciliter.

So in this group with a very well-controlled LDL cholesterol, the higher your HDL cholesterol level on treatment, the lower the cardiovascular risk and vice versa. But low HDL cholesterol doesn't seem to account for all of the cardiovascular risks that remain, so we need to look at the remaining lipid, and that's the evidence indicating triglycerides.

This is a meta-analysis of 29 trials, published in Circulation 2007. It's depicted on this slide, showing that higher levels of triglycerides are associated with increased cardiovascular risk, and this holds true in both

males as well as females. And even after adjustment for HDL cholesterol, which is collinearly related, this risk persists.

I want to show you the prove it to me 22 study, and this examined the impact of intensive versus standard statin therapy in patients after an acute coronary syndrome. When stratified by on-treatment triglyceride levels, those patients with triglycerides less than 150 had a 27 percent lower incidence of cardiovascular events compared to the group who had triglycerides on treatment, greater than 150 milligrams per deciliter.

So I think, really, the question is, how has this data been presented to the clinician? So what do we do when we see patients every single day in our office? What are we supposed to do with it? I think the National Cholesterol Education program, Adult Treatment Panel III, also referred to as the NCEP-ATP III, have set goals of LDL cholesterol as the primary target of less than 100 milligrams per deciliter for patients with coronary heart disease or a CHD risk equivalent.

Now, once the LDL cholesterol is controlled, if patients have triglycerides above 200 milligrams per deciliter, non-HDL cholesterol becomes the secondary target of treatment. And non-HDL cholesterol goals are set at 30 milligrams per deciliter more than the patients' LDL cholesterol goal.

Now, while there are no explicit goals defined for triglycerides or HDL cholesterol, an HDL cholesterol level of less than 40 milligrams per deciliter is considered low and is a categorical risk factor, and a triglyceride value of less than 150 milligrams per deciliter is considered as normal.

So the real question is what do the guidelines tell us about the management of triglycerides and HDL? First, for triglycerides greater than 500 milligrams per deciliter, to prevent pancreatitis, therapy with a fibrate or niacin is recommended.

For triglycerides between 200 and 499 milligrams per deciliter, intensification of

statin therapy is recommended first, and the addition of a fibrate or niacin can be considered. For HDL less than 40 or triglycerides of 150 to 199 with an LDL cholesterol of between 100 and 129, intensification of therapy with a statin is recommended and the addition of a fibrate or niacin can be considered.

Now, all of this was emphasized again in the NCEP 2004 update. So what I'm going to do is, I'm going to examine what the clinician has available currently as treatment options to target triglycerides and HDL cholesterol. And those are going to include marine-based fish oils, niacin, and fibrates.

For fish oils, the marine-based products are EPA and DHA based, and the only approved indication for patients with triglycerides is about 500 milligrams per deciliter. Now, the only cardiovascular outcomes data for a fish oil/statin combination treatment is the JELIS trial, and this was conducted exclusively at a Japanese population and utilized a background of low-dose statins.

Now, niacin is the other available treatment for triglycerides and HDL. It also has limited cardiovascular outcomes data, especially when used in combination with a statin. However, there are two large-scale cardiovascular outcomes trials, one, the AIM High, and the other, HPS2 Thrive, that are currently underway, and they are both evaluating a niacin/statin combination treatment versus maximal statin alone.

We look forward to these data on several levels because clinicians at first are concerned primarily for the potential of an adverse effect of niacin on compliance, which is a long-term issue due to the flushing issue that niacin has. And I think they're worried a little bit about the effect niacin may have on glucose and uric acid levels, especially in their patients who have diabetes, or are at risk for diabetes, or who may have a history of gout.

Now, fibrates are the third triglyceride HDL-focused therapy option. Of course, you've seen the data with gemfibrozil, which demonstrated

positive cardiovascular outcomes in the Helsinki Heart Study and the VA-HIT. Fenofibrate has shown a positive impact on cardiovascular outcomes in patients with elevated triglycerides and low HDL in both the FIELD and the ACCORD Lipid. In addition, fibrates may be the preferred treatment in patients who have suboptimally-controlled diabetes, or high uric acid levels, or a history of gout.

Now, I'd like to look at the baseline lipid values in the ACCORD Lipid. The mean LDL cholesterol is approximately 100 milligrams per deciliter. The mean HDL was 38 and the median triglyceride was 162. Now, if you were to look at the NEC-ATP III guidelines, on average, these patients in ACCORD Lipid would not have been considered for the addition of either a fibrate or niacin to their statin therapy.

I'd like to take a moment to examine women and tell you that, first of all, women with diabetes have substantial cardiovascular risk. And I think the ACCORD Lipid clearly demonstrated that there is a benefit of fenofibrate and simvastatin

combination treatment in women if they have elevated triglycerides and low HDL cholesterol. Of note, neither fish oil nor niacin have demonstrated a similar benefit in female patients with diabetes, actually any patients with diabetes.

Additionally, fenofibrate has benefitted beyond cardiovascular risk reduction in patients with diabetes, and these benefits are especially prominent in the kidney and in the eye. And you've heard some of that already. I believe both the ACCORD Lipid and the FIELD demonstrate a benefit in reducing progression to proteinuria. I think, interestingly, the reduction in proteinuria in ACCORD Lipid was seen in addition to the fact that many patients were taking ACE inhibitor therapy and had good glycemic control.

In terms of the benefit to the Eye, fenofibrate has been demonstrated to slow the progression to diabetic retinopathy and reduce the need for laser therapy in diabetics in both the FIELD and the ACCORD Lipid. Now, this is important to recognize that this is a novel benefit of

fenofibrate. And this is a very important quality of life consideration for those clinicians who treat patients with diabetes because there are very, very limited treatments to prevent this problem.

So I think, in clinical practice, physicians who often treat high-risk patients will obviously have a lot of patients with mixed dyslipidemia. And many of these patients are obese or overweight. Many of them have diabetes or are at risk for diabetes.

So I'm going to show you a clinical scenario. This is a 55-year-old women who has diabetes, who weighs 150 pounds. Her blood pressure is well-controlled. Her medications include metformin, an ACE inhibitor, and a statin. Her pertinent laboratory values include a hemoglobin A1C of 6.8 percent. She has a normal eGFR and a high microalbumin. Lipid values reveal a total cholesterol of 180, LDL of 90, triglycerides of 250, an HDL of 40.

Her calculated non-HDL cholesterol is 140,

which is certainly more than 30 milligrams per deciliter above her LDL cholesterol and is discordant with her LDL cholesterol. So when you look at her, she is at or near goal for blood pressure, hemoglobin A1C, and LDL cholesterol. However, she is not at goal for non-HDL cholesterol.

So to meet the ATP III guidelines, among the treatment options to achieve that non-HDL cholesterol goal, fish oil, niacin, and a fibrate such as fenofibric acid could be considered. Gemfibrozil would not be considered, in my opinion, because it's not an appropriate option because of the well-known effect that gemfibrozil has on increasing statin blood levels, maybe placing a patient at higher risk for muscle-related adverse events.

So in this woman, triglycerides and HDL abnormalities persist despite adequate statin therapy. In the presence of type 2 diabetes with evidence of microvascular complications, I think that that drives the therapeutic choice towards

fenofibric acid as the most appropriate treatment option. And that is exactly what I gave this woman.

So I'd like to show you what I think are the treatment options clinicians face, and this is based on clinical experience, as well as clinical trial data, and talking with many of my lipid colleagues over the years.

I think that when you look at patients who are on a statin and an LDL cholesterol goal who have mixed dyslipidemia, for the group who have triglycerides in the middle here that are less than 200, but who have low HDL cholesterol as less than 40, I think niacin would be a treatment option. It is the best drug to raise HDL regardless of baseline triglycerides.

I think, down below that, if your triglycerides are high, greater than 200 milligrams per deciliter, and you have low HDL cholesterol, I think fenofibrate or fenofibric acid would be your most appropriate choice because they're very effective, at least, the fibrates are, in lowering

triglycerides and raising cholesterol under these situations, and you get great compliance and tolerability over the long haul.

Now, over on the far side, it's usually uncommon that you get just high triglycerides under normal HDL, but if you do, you don't really have to worry so much about the HDL side; Just do something that lowers triglycerides. At that point, now fish oils become an option as well as niacin and fibrates. And I think that's the way most of us in the clinic would treat patients under these mixed dyslipidemia situations when they're on a statin to maximal LDL goal.

So what I think the ACCORD Lipid brings to our body of knowledge regarding the use of fibrates is, first, it confirms that fenofibrate decreases cardiovascular events in both men and women with diabetes who have high triglycerides and low HDL cholesterol who are receiving tolerable statin therapy.

Second, these benefits would be anticipated across the entire spectrum of insulin resistance in

patients who have these persistent lipid abnormalities.

So overall, I think fenofibrate and fenofibric acid are important therapeutic options for the practicing clinician, especially in the treatment of patients with persistent mixed dyslipidemia after statin treatment.

I also think the additional demonstrated microvascular benefits in patients with diabetes are very important considerations for the clinician. Thank you very much.

Sponsor Presentation (continued)

James Stolzenbach

DR. STOLZENBACH: Thank you, Dr. Jones.

I'd first like to just summarize briefly the benefit-risk profile of fenofibrate and fenofibric acid, starting with the risks. ACCORD Lipid has not changed our evaluation of the risk for hepatic or pancreatic events. The study provided additional data regarding the increase in creatinine, which has been shown to be reversible and not associated with renal harm. Rhabdomyolysis

has been reported with fibrate and statin monotherapy. The incidence is higher with coadministration therapy, but it is still a rare event.

The number needed to harm for coadministration therapy, as compared to statin monotherapy, is between 11,000 and 18,000 patients treated for one year. Muscle-related adverse events are appropriately described on the label and in our medication guide.

Turning to the benefits of fenofibrate and fenofibric acid, consistent with the data from prior trials, ACCORD Lipid has demonstrated that fenofibrate reduces cardiovascular risk in patients with high triglyceride and/or low HDL. In this high-risk group, the number needed to treat to prevent one cardiovascular event was 20 over 4.7 years. Additionally, there was no observed treatment by gender interaction in the persistently dyslipidemic group.

In patients with diabetes, fenofibrate has demonstrated important microvascular benefits in

both FIELD and ACCORD, and in particular, the retinopathy benefits were observed in specific substudies in both trials.

So in light of this benefit-risk overview, Abbott proposes to clarify the coadministration indication for Trilipix with the addition of information to better define the definition of mixed dyslipidemia. In addition, Abbott proposes to add details of the ACCORD Lipid trial to the prescribing information. These details would include the primary outcome, the results by gender, and the results by pre-specified subgroup of dyslipidemia.

Now, the FDA has asked the committee two questions today, and these are to consider regarding not only the ACCORD Lipid study but also the indication for coadministration of Trilipix with a statin. Before we conclude our presentation, we'd like to briefly discuss the first question the FDA has posed. It asks you to consider regarding the conduct of a cardiovascular outcomes trial.

We can all agree that patients without high triglycerides and/or low HDL do not receive cardiovascular benefit from fenofibrate therapy. ACCORD Lipid and FIELD both confirmed that there is no need to evaluate patients with normal triglycerides and HDL in another cardiovascular outcomes trial. It's already well-established that there is no cardiovascular benefit to either men or women if they do not have abnormalities in these baseline lipid values.

This brings us to the consideration of conducting a trial with patients with high triglycerides and/or low HDL in patients that have well-controlled LDL cholesterol on statin monotherapy. The data available to us today demonstrate that these patients are at relatively high risk for a future cardiovascular event. The ACCORD Lipid trial also shows us that these are exactly the same patients who could potentially benefit from fenofibrate therapy, and indeed did benefit in ACCORD Lipid. In a new trial, half of the patients that would have low HDL and high

triglycerides after statin monotherapy would still be put on a placebo for approximately five years while that trial is conducted.

So although conducting another trial should reduce the uncertainty of the magnitude of benefit in dyslipidemic patients, it also raises the question of not treating half of the patients in the trial for their triglyceride and HDL abnormalities when they're on statin monotherapy with well-controlled LDL.

Consideration must also be given to the limited options that currently exist for physicians when they're attempting to treat patients with abnormalities in triglycerides and HDL, despite very good LDL control. The conduct of a trial, analysis of the results, and a regulatory review would probably occur over approximately a seven- to eight-year period. How do we appropriately guide physicians to treat these patients based on all the data that we currently have available to us today? As we discuss these questions, we confirm that Abbott is committed to working with the FDA to

ensure a final decision that meets the needs of both physicians and patients.

So to summarize, based on our review of the data, Abbott concludes that the overall benefit-risk profile of fenofibric acid and fenofibrate is positive in patients with elevated triglycerides and low HDL. Prescription data demonstrates that physicians are currently identifying these patients correctly when considering fenofibrate therapy. The Trilipix label correctly identifies patients that derive cardiovascular benefit and appropriately represents the safety profile.

So on behalf of Abbott Laboratories, I'd like to thank you very much for your attention during our presentation.

Clarifying Questions from Committee to Sponsor

DR. GOLDFINE: Thank you very much for the concise presentation. I think we will now open it for clarifying questions from the committee for the sponsor, and we'll start with Dr. Heckbert.

DR. HECKBERT: Yes. Thank you. I have a question for Dr. Stolzenbach. And that is, in your

slide 115, you indicated that the company is interested in clarifying the coadministration indication. I'd like to ask you, what clarification would you make to that indication?

DR. STOLZENBACH: Well, currently -- could I have the indication put on the screen, please, from our core presentation?

Currently, as you can see from our indication, it states that an adjunct to diet in combination with a statin to reduce triglycerides and increase HDL cholesterol in patients with mixed dyslipidemia, but there's really no comments about what that is, whether that's high triglycerides or HDL, and what type of values are there.

So from our perspective, we would like to clarify that patients that have low HDL and high triglycerides would be the patients considered for therapy.

DR. GOLDFINE: Thank you.

Dr. Veltri?

DR. VELTRI: I'm still unclear as to the sponsor's position as to whether or not these

trials have truly confirmed the clinical outcome benefit. Even if you were to use it in the patients that it's currently indicated for -- that is dyslipidemic patients who are CHD equivalent like diabetes or true CHD patients -- because I think, as opposed to LDL and hypertension, where maybe those are more validated surrogates, even though there's strong epidemiologic data, and certainly these hypothesis-generating findings in these two trials suggest that indeed, there is clinical benefit, I think that opens the door, perhaps, to some concerns as to whether there clearly is clinical benefit, because, obviously, these patients are being treated ultimately not to fix a number but to improve CVD death, MI, and stroke. So it's not quite clear to me.

Is the sponsor planning to do a clinical outcome trial based on these data, or are you just waiting for the vote this afternoon and the FDA's input?

DR. KELLY: In response to your first question about the level of data that is currently

available to us, we believe that the consistency of the results from ACCORD Lipid and FIELD with fenofibrate monotherapy, and now with fenofibrate in coadministration with a statin, and in the greater context of the other fibrate studies, demonstrate a very clear patient population that has consistently derived benefit; that is, the patients with elevated triglycerides and low HDL.

So, yes. With the body of data available to us today about the benefit of fibrate therapy, and when you limit it just to fenofibrate therapy and look just towards ACCORD Lipid and FIELD, we believe that the evidence is very convincing of the benefit that is derived in those patients with elevated triglycerides and low HDL, and that the patients that do not demonstrate those lipid abnormalities do not derive significant benefit.

As far as the second portion of your question, related to a cardiovascular outcomes study, as Dr. Stolzenbach spoke to that, there are important considerations for discussions of a cardiovascular outcomes study, and part of that

discussion is the purpose of the meeting that we're here today to discuss. So we look forward to the input of the panel regarding that matter.

DR. GOLDFINE: Thank you.

Dr. Weide?

DR. WEIDE: Thank you. It looks like the majority of the improvement in the studies, particularly ACCORD Lipid, is from improvement in HDL. We can argue about the triglycerides. The problem with the data is we don't have levels of triglycerides as we go up. We don't have 200 versus 400 versus 700 or anything like that.

So that's a little concerning, and maybe is the reason for a trial. But if the majority of the impact is from the HDL, with the recent concern of some patients having a decrease in their HDL, my question is about the fibrates that cause a decrease in HDL.

Do we know what percentage that is? Do we know why that occurs? Is there any way to identify the patients who would actually have a decrease in their HDL rather than an increase in their HDL?

Because we'd all say that's a bad thing to have occur.

DR. KELLY: As far as the first part of your question, concerning whether low HDL identified the patient population that derived benefit more so than elevated triglycerides, I will point out that we saw benefit along the continuum of both lowering of HDL and increasing triglycerides.

Indeed, you can define populations by a variety of different combinations of HDL and triglycerides, and still see that evidence of that pattern of benefit that exists across the continuum for both triglycerides and HDL.

As far as the second portion of your question, which is about paradoxical HDL lowering, this has been reported rarely in association with all fibrates, not just fenofibrate, and was rarely reported within ACCORD Lipid, and was very rarely seen in our Trilipix clinical program. There were four total cases in patients not receiving thiazolidinediones and four cases in patients receiving thiazolidinediones, in which they had

significant decreases in HDL observed with the combination of fenofibrate.

So, yes, these rare occurrences have been reported. The mechanism is unknown for these, but, obviously, they're very easily monitored, reversible with discontinuation, and there is no association with any other adverse events that we're aware of.

DR. WEIDE: And no way to pre-identify these patients?

DR. KELLY: Not that we're aware of.

DR. GOLDFINE: Thank you.

Dr. Brittain?

DR. BRITTAIN: Yes. A couple questions about the analyses in women. First of all, the first question is, about how many women are actually in these really small subgroups, what I think are pretty small subgroups by arm when we're getting down to the dyslipidemia subgroup, especially with baseline statin. I'm guessing there are only about 60 per arm, something like that, but I'd like to hear that.

Also, in terms of presenting the data about the women, you have presented a lot of information. But I would be interested in seeing it in a slightly different format, and I wonder if you have this, where you have the results by arm for the women who have dyslipidemia and then the complement of that as well, the two lines, the mutually exclusive groups, unlike the way you presented it before, and confidence intervals of the hazard ratios in both those subgroups.

DR. KELLY: So in response to your first question, you are correct. In that 3D bar chart that I showed in the core presentation for women only, with the simvastatin arm and the coadministration arm, some of those bars did represent small sample sizes, especially with the more severe degrees of dyslipidemia. Some of those bars were small, as far as the number of patients included in those treatment groups, and represented by the various HDL and triglyceride thresholds.

As far as the second part of your question, Dr. Ginsberg showed a slide.

If I can have the slide that was up on the preview back again, and I'll show you this slide.

So this is for the women with dyslipidemia and by gender in those without dyslipidemia. And so you can see the hazard ratio and the confidence intervals are represented there, as well as the event rates and sample sizes for those different groups.

DR. GOLDFINE: Thank you.

Dr. Hiatt?

DR. HIATT: Just going back to understanding your overall logic and the conclusions you'd like us to take, that in a negative trial, the gender interaction was the only significant subgroup interaction, but that goes away if you look at the dyslipidemia patients. Right? In the overall subgroup look, the dyslipidemia patients was not as significant an interaction, but that's where you see all the benefit.

I also want to point out that in your briefing documents, section 4511, your justification for looking at prior statin use as a

meaningful subgroup analysis was not a pre-specified subgroup in the primary trial. Correct?

DR. KELLY: That's correct.

DR. HIATT: Your rationale is, it's consistent with guidelines?

DR. KELLY: And the Trilipix prescribing information as well.

DR. HIATT: Okay. So the conclusion I think I just heard, then, was that based on this kind of information, there'd be loss of equipoise to conduct another randomized controlled trial in this responsive subgroup?

DR. KELLY: I think that it's a consideration for the comfort level of clinicians for proceeding with an outcomes study. It's a consideration to leave triglycerides and HDL untreated in a patient with demonstrated excellent LDL control, but with residual substantial triglyceride and HDL abnormalities. That's the question.

DR. HIATT: So just so I understand that, you think actually running a trial to answer a

question based on the current level of evidence would lose equipoise or would it just be hard?

DR. KELLY: Represents some challenging considerations. It does represent some challenging considerations, both on a clinical level and on a study conduct level.

DR. HIATT: Okay. Because if you think that there's loss of equipoise, and you think it's unethical to do such a study, you're already convinced that it works in the subgroup.

DR. KELLY: We believe that the body of evidence available between ACCORD Lipid and FIELD demonstrates a substantial and convincing body of evidence for treatment with a fenofibrate in that group of patients.

DR. HIATT: So we don't need a trial like that?

[No response.]

DR. GOLDFINE: Okay. Thank you.

Dr. Cooper?

DR. COOPER: I have a question for Dr. Kelly about the epidemiologic studies of rhabdomyolysis

shown on, certainly, slide 71 that you showed earlier. In that slide, you show us a really striking difference in the rate of rhabdomyolysis between the analysis by Graham and the analysis that was done by i3, even when you exclude the cerivastatin exposures.

It looks like, in reading through the FDA briefing document, that the i3 analysis required evidence of renal insufficiency, whereas Graham did not. And it's not clear, when I look at the agency's case definition that was also described in the briefing book, it doesn't look like the agency requires renal insufficiency for their case definition of rhabdomyolysis.

So two questions. One is that, can you give us a rationale for why the i3 analysis required renal insufficiency? Because that would seem to exclude several cases that might be clinically important. And two, did you do an analysis with a definition more closely aligned with the FDA's definition to help us understand a little bit more about the risk of rhabdomyolysis to allow some

comparison?

DR. KELLY: I'm going to invite Dr. Embrescia to approach the podium, from our pharmacovigilance group. But I wanted to state that that requirement reflected the case definition for rhabdomyolysis that has been brought forward by the ACC, AHA, NHLBI statin advisory. So the inclusion of the renal requirement into that definition reflected contemporary availability of the guidelines related to that, but I'll let Dr. Embrescia answer the rest of the question.

DR. EMBRESCIA: Jim Embrescia, Global Pharmacovigilance. As Dr. Kelly said, the original study was done internally to Abbott, and then when we did our second study, it was a part of a postmarketing commitment as a request of the FDA. And the protocol was reviewed with the FDA, and comments were provided by them. The definition for rhabdomyolysis did come from an article that was published by the AHA around 2002, probably sometime post-Dr. Graham's initiation of his study. So we believed that that was the appropriate population

to utilize for the study.

We did actually do a sensitivity analysis to try and look at that, and we used a 50 percent marker, which showed us that the relative risk essentially didn't change. It went up to about .49 percent with a 50 percent sensitivity analysis; with 100 percent, went up to about .69 percent, so, again, consistent with what Dr. Graham showed and what our study showed. And as you mentioned, the numbers do look different, although the confidence intervals overlap quite a bit.

DR. GOLDFINE: Thank you.

I believe this is our last question. Dr. Gregg?

DR. GREGG: I think the previous questions may have answered this, but I'll ask it anyway just for clarification. The sensitivity analyses that you presented are comforting on the one hand, because they indicate that the higher-risk women have a relative protection. But this implies that, given that the overall trial is showing 1.3, 1.4, that then there are some other women that actually

have a higher risk than that average, that maybe isn't reflected in the point estimates we've been seeing. And I'm wondering whether any of these analyses have identified who those women are? Is there a subgroup where in there clearly should be an indication that this is a bad drug for them, and who that may be?

DR. KELLY: Well, we're committed to ensuring that the proper and appropriate women receive the drug, so, clearly, non-dyslipidemic women, just like non-dyslipidemia men, should not be receiving fenofibrate therapy or fenofibric acid therapy added to a statin. But the data we reviewed today demonstrate that there was no treatment by gender interaction in the dyslipidemia subgroup, the appropriate patients who we believe derive benefit from the therapy.

So we want to work with the FDA to ensure that our label contains appropriate information from ACCORD Lipid about the results to further guide the prescriber to ensure that only appropriate patients receive the therapy.

DR. GOLDFINE: We've had a few additional questions come in. Dr. Kaul?

DR. KAUL: Thank you. I would like to echo what Dr. Hiatt said, that, in my opinion, the data are neither clear nor convincing that there is a benefit in the subgroup of dyslipidemic individuals.

I would like to draw your attention to slide 31 to sort of illustrate this point. If you look at the Helsinki Heart Study, in the dyslipidemic group, there's a 78 percent reduction in outcomes versus a 20 to 25 percent in those that are not dyslipidemic. Unusually large treatment effects in a small subgroup are likely implausible and raise the suspicion of the play of chance. They're likely to be spurious.

Now, if you look at all other individual trials, there is a considerable overlap in the confidence intervals. The only confidence interval where there is no overlap is the pooled estimate. And I will submit to you that there is sufficient clinical heterogeneity in these trials that, in my

opinion, preclude pooling. I mean, you have primary prevention, secondary prevention, mixed studies. You have diabetic, non-diabetic. You have statin background, no statin background. I don't think you can do that.

So that's the point that I want to make, is that so far, the data that you have shown to us is hypothesis generating, not hypothesis validating.

The question I have for you is that in slide 61, you showed us retinopathy data. Do you have any hard outcome? I don't know what this progression of retinopathy means or laser treatment means. Do you have any data for vision loss?

DR. KELLY: There was data for vision loss in the ACCORD Eye substudy that was an endpoint that was evaluated. I don't believe we have a backup slide on the endpoint of vision loss, but I can check with my team and see if we can get that for you.

DR. KAUL: What about other microvascular outcomes? What about the heart outcomes in terms of nephroprotection? You showed us data for

microalbuminuria, and, again, I don't know what the relevance of that is.

DR. KELLY: So we have data from ACCORD Lipid, and the core slide on renal had both. We had the numeric values for the tech slide.

DR. KAUL: While you are at it, do you know how many subgroup analyses were done? Because that pertains to this progression of retinopathy. Dr. Ginsberg said the p value of .006. First of all, I don't think a subgroup of a subgroup of a subgroup warrants a p value analysis. But if you have a p value of .006 and you have 19 subgroups, which is what the briefing document states, the adjusted p value is .11.

So the point I'm trying to make here is I'm trying to understand what the clinical relevance of these surrogate endpoints are. I'm not quite sure whether these are validated, and the statistical methodology is also quite shaky in drawing these so-called clear and convincing conclusions.

DR. KELLY: In response to your question, Dr. Kaul, on the hard endpoints for renal, I did

put up core slide number 75, in which for both ACCORD Lipid and FIELD, we show that the reported number of patients that progress to a diagnosis of end-stage renal disease or need for dialysis.

So you're right. While proteinuria is an intermediate marker that is associated with risk for progression of renal disease as well as cardiovascular risk, there was also reported for both these studies hard renal endpoints related to need for dialysis.

In response to your earlier questions concerning the level of the strength of the data, I'd like to invite Dr. King to come to the podium to respond to that portion of your question.

DR. GOLDFINE: While Dr. King is coming to the podium, Dr. Ginsberg has requested to make a comment that the panel is going to allow.

DR. GINSBERG: Yes. Dr. Kaul, I think it's a misstatement to say that the ACCORD Eye study had 19 subgroups. The subgroups in the ACCORD Eye study were a blood pressure subgroup across two glycemic arms, a lipid subgroup across two glycemic

arms, and two glycemic arms. So the p value of .006 corrected by what you want, 3 or 6, would still be significant.

DR. GOLDFINE: Thank you for that clarification.

Dr. King?

DR. KING: Hi. My name is Marty King. I'm a statistician with Abbott Laboratories. I wanted to touch on the issue of heterogeneity on the analysis shown here in the patients with elevated triglycerides and low HDL. There was no statistical heterogeneity across all five of these studies, nor if we took HHS out. But there's no reason, based on the test of heterogeneity, to believe that the HHS study was different from the other studies.

Then with regard to the overall level of evidence, we've talked -- there's been discussion of subgroups. I think if we were here to take ACCORD Lipid and try to decide whether to approve a new drug on this basis or a new indication for a drug on that basis, then I think the discussion of

subgroups would be right on. But if our goal is to relate ACCORD Lipid to the Trilipix label, then the Trilipix label represents the pre-defined group of patients in whom the hypothesis exists.

So the ACCORD Lipid label doesn't identify a specific population of patients for treatment, but we can look at the language on the label and look at the language in the guidelines, and ask, who are the patients who are generally considered appropriate for coadministration treatment?

This slide shows a variety of groups based on HDL and triglyceride cutoffs for patients who are receive a statin at baseline. Some of the groups represent HDL cutoffs only, some of the groups represent triglyceride cutoffs only, and some represent both. And if we were to go back before ACCORD Lipid was unblinded and define a population who would be appropriate for coadministration treatment, then that population represents our primary hypothesis for ACCORD Lipid.

So each of us might demonstrate that or might define that population a little bit

differently, but as shown in the analyses on this slide, regardless of how you might reasonably define that population, you get a group of patients who, in ACCORD Lipid, had a significant reduction in cardiovascular risk.

DR. GOLDFINE: Thank you. If we can keep the questions and answers brief, we can get to two final questions. Dr. Heckbert?

DR. HECKBERT: Yes. This is a question for Dr. Colman, and it has to do with how the FDA -- what the policy is about coming up with indications for lipid-lowering drugs in the modern era. The indications for this drug, I guess, were written in 2008. Is that right?

DR. GOLDFINE: I'm sorry.

Dr. Colman, do you want to take that after? Because it's really not directed specifically to the presenters on hand, and we'll bring that right after lunch.

Final question, Dr. Weide?

DR. WEIDE: Actually, I don't have a question. I was just going to help my friend,

Sanjay.

It is totally appropriate, I think. All the diabetes studies look at a progression of three levels of retinopathy, and that is accepted as an indication of improvement or decay in that case. So that's a very, very standard, typical way to look at it. Microalbuminuria is also a very typical standard way to look at diabetes issues.

So I think those were both appropriate. We can argue about what they mean, but they're appropriate cutoffs.

DR. KAUL: But my comment was in the context of this trial; is this ACCORD trial really designed to address what the impact on renal function is going to be when right at the very outset, you are sanitizing the population?

DR. WEIDE: No. I don't think it is.

DR. GOLDFINE: Thank you for the discussion. We will now break for lunch. We will reconvene again in this room in one hour, which is 12:30 p.m. Please take any personal belongings you may want with you at this time. The ballroom will be

secured by the FDA staff during the lunch break.

Panel members, please remember that there should be no discussion of the meeting during lunch amongst yourselves or with any members of the audience. Thank you.

(Whereupon, at 11:37 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:29 p.m.)

DR. GOLDFINE: So that we can get started on time, I'd like to invite everybody back to their seats.

There was one question left over regarding the Eye findings, but we're going to wait until after the FDA presentation. So we will now proceed with the presentation from the Food and Drug Administration. I would like to remind the public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. Thank you.

FDA Presentation – Vicky Borders-Hemphill

DR. BORDERS-HEMPHILL: Good afternoon. My name is Vicky Borders-Hemphill. I'm a drug use analyst in the Office of Surveillance and Epidemiology.

Today, I will describe the projected number of patients with a fibrate or a statin prescription claim from a prescription dispensed in the

outpatient retail setting over the past four years. I will provide the number of patients with concurrent claims from these two markets per year and by product per year. I will describe the demographics of patients with concurrent Trilipix and statin claims. I will describe the limitations of this analysis and summarize the findings.

Proprietary drug use databases licensed by the agency were used to conduct this analysis. For national estimates and concurrent drug analyses, we used Wolters Kluwer Health Source Lx database. This is a longitudinal patient data source for prescriptions and medical claims. Since these data are from commercially insured, Medicare Part D, Medicaid, and cash payers, the elderly population aged 65 years and older is adequately represented.

The patient population was selected based on the occurrence of one fibrate or statin claim per year, with a duration of therapy of at least one day from the outpatient retail setting, excluding mail order pharmacies. Patient eligibility criteria were not applied to this study, meaning

that a patient only had to occur one time and not at separate points in time, for example at the beginning and end of the study period.

An episode of concurrency is identified when a patient has a prescription claim from the fibrate market that overlaps with a day's supply for a prescription claim for drugs in the statin market without regard to fill order. The day's supply was calculated by adding the estimated number of therapy days to the date of prescription dispensing.

A grace period of 50 percent was allowed for the day's supply time window to adjust for undercompliance or delays in prescription filling. The number of therapy days is estimated by the dispensing pharmacist by dividing the number of tablets or capsules dispensed by the number of tablets or capsules consumed per day. Thus, the total days of therapy for a claim with a 30-day supply would be 45 days when including the 50 percent grace period.

We obtained the number of projected unique

patients during each calendar year from the year 2007 through year 2010 with a 90-day lookback period, which is the number of days to look back for a prescription claim before the study-begin date.

Listed here are the fibrate products included in the study. We looked at these products as one group representing the fibrates and additionally focusing on Trilipix utilization. Listed here are the statin products included in the study. We look at these products as one group representing the statins and additionally by product and product strength.

For this and all subsequent slides, the year that the patient filled the prescription is on the X axis and the projected number of patients with a prescription claim is on the Y axis. This slide depicts the absolute number of patients in millions with a prescription claim for a fibrate in light blue or a statin in dark blue, from year 2007 to year 2010.

During this entire study period,

approximately 9.1 million patients had a fibrate claim and 68.4 million patients had a statin claim, which includes single-ingredient and combination products. The number of patients with a fibrate claim increased by 34 percent from 3.7 million patients in year 2007 to 5 million patients in year 2010, while the number of patients with a statin claim increased by 27 percent from 32.7 million patients during year 2007 to 41.5 million patients during year 2010.

This slide shows the total number of patients in millions with a prescription claim for a statin in the dark blue bars and by the top five products in the statin market per the line. Simvastatin generic was approved in year 2006 and accounted for the increase in market share, as shown here from year 2007 to year 2010.

Around 30 to 48 percent of patients with a claim for a statin were for simvastatin, 19 to 35 percent were for atorvastatin, followed by rosuvastatin, pravastatin, and lovastatin. From year 2007 to year 2010, patients with a claim for

atorvastatin decreased by 30 percent, while simvastatin increase by 101 percent, rosuvastatin by 53 percent, and pravastatin by 145 percent.

This slide depicts the number of patients in millions with a prescription claim for a product in the fibrate market. Around 58 to 70 percent of patients with a claim for a fibrate were for a product in the other fenofibrate group. Twenty-nine to 34 percent were for gemfibrozil and 15 to 19 percent were for Trilipix.

Trilipix was approved in December 2008, when Trilipix utilization increased by 30 percent from 724,000 patients in year 2009 to 940,000 patients in year 2010 and accounted for the increasing fibrate market share during that time. Please note that unique patient counts were obtained per product and that a patient may have been switched from one fibrate to another during the year. Thus, the yearly proportions do not sum to 100.

Shown here are the numbers of patients in millions with concurrent claims for both a fibrate product and a statin product shown in the blue bar,

as well as the number of patients with concurrent Trilipix and statin claims in the gold bar.

For the overall number of patients with concurrent claims for a fibrate and a statin, there was a 48 percent increase from 1.6 million patients during year 2007 to 2.4 million patients during year 2010. Of these patients with concurrent fibrate and statin claims, 14 to 19 percent had a fibrate claim for Trilipix.

The number of patients with concurrent claims for Trilipix and a statin increased by nearly 50 percent from 313,000 patients in year 2009 to 467,000 patients in year 2010, and contributed to the increasing concurrent fibrate statin market share during that time, which increased by 6 percent from 2.3 million patients in year 2009 to 2.4 million patients in year 2010.

Shown here are the total number of patients with a Trilipix claim in the blue bar, as well as the number of patients with concurrent Trilipix and statin claims in the gold bar. Of the nearly 724,000 patients in year 2009 with a Trilipix

claim, around 313,000 patients, or 43 percent, had a concurrent claim for a statin. And of the 940,000 patients in year 2010, around 467,000 patients, or 50 percent, had a concurrent claim for a statin.

During year 2010, the greatest proportion of concurrent claims with Trilipix were for simvastatin at around 36 percent of patients, followed by rosuvastatin, then atorvastatin, pravastatin, and Vytorin.

We also looked at the number of concurrent claims with Trilipix and a statin by strength. And the greatest proportion of concurrent claims was for simvastatin 40 followed by rosuvastatin 10, simvastatin 20, rosuvastatin 20, and simvastatin 80. For patients with a prescription claim for Trilipix concurrent with a prescription claim for a statin, we examined gender. Females accounted for around 40 percent of patients.

Limitations of these analyses were that mail order was excluded because the universe of mail order and specialty pharmacies contributing to

these data are unknown, and national projections for mail order data are not available at this time. Mail order pharmacies typically dispense chronic use medications in larger quantities than retail pharmacies. Therefore, we believe that the omission of mail order may underestimate the absolute and concurrent numbers of patients. According to IMS Health, around 25 percent of fibrate and 27 percent of statins were sold to mail order channels of distribution.

Also, when reviewing these data, please note that unique patient counts may not be added across time periods due to the possibility of double-counting patients. No statistical tests were performed to determine statistically significant changes over time or between products. All changes should be considered approximate and may be due to random error.

Using these data, several assumptions are made: that a patient is taking the prescription as recommended and the day's supply for a prescription is recorded to reflect how the patient is actually

taking the prescription. These data do not provide the indication for use of these products; for example, treatment of severe hypertriglyceridemia versus other lipid disorder indications. Further study with medical records validation is required to determine appropriateness of therapy or indications for use.

So in summary, during year 2010, use of statins was high in the U.S. And about eight times the number of patients had a prescription claim for a statin compared to a fibrate. Around 41.5 million patients had a statin claim and 5 million had a fibrate claim.

Of the 940,000 patients with a Trilipix claim in year 2010, around 467,000, or 50 percent, had a concurrent claim for a statin. Trilipix, absolute and concurrent utilization increased by 30 percent and 50 percent respectively from year 2009 to year 2010 and contributed to the increasing fibrate national utilization and fibrate concurrent use with statin market share.

Most concurrent claims with Trilipix were

for simvastatin, followed by rosuvastatin, and most concurrent claims were for simvastatin 40, followed by rosuvastatin 10. Of the concurrent Trilipix with statin claims, females accounted for around 40 percent of patients. Thank you.

DR. GOLDFINE: Thank you. As the next speaker comes up, we're going to take all FDA questions at the end.

FDA Presentation – Christian Hampp

DR. HAMPP: Good afternoon. My name is Christian Hampp. I'm an epidemiologist at the Office of Surveillance and Epidemiology.

Today, I present observational evidence about drug safety of combination statin and fibrate use. I will start with presenting the postmarketing requirement for Trilipix. Then I will present the FDA observational study by Graham and colleagues. Next, I will present our assessment of the i3 study that was referred to by Dr. Kelly as i3 study number 2. This study was part of the Trilipix postmarketing requirement. And, finally, I will present the i3 study with

additional safety outcomes that was referred to as i3 study number 1 because it came temporarily earlier.

This is the postmarketing requirement. The FDA required the sponsor to conduct an observational study to estimate the incidence and risk factors for hospitalized rhabdomyolysis in patients treated for the fibrate in combination with a statin versus statin of fibrate monotherapy. The FDA recommended methodology used by Graham, et al.

To provide a brief summary of the Graham study, they used an inception cohort that is a new user design based on data from 11 U.S. health plans. The study period was from '98 to the middle of 2001. They required 180 days' baseline period free of drug use for each exposure cohort and calculated exposure based on days of supply of each prescription, plus 30 days. The outcome was hospitalized rhabdomyolysis, identified from claims data and validated from medical record review.

Briefly, these are the findings. The study

consisted of a quarter million patients with about 225,000 person years of monotherapy and 7300 person years of combined therapy. They had 194 potential cases and 24 out of them were confirmed cases of hospitalized rhabdomyolysis.

These are the results. Most outstanding finding is from the cerivastatin alone or in combination with gemfibrozil. And we see that in findings for statins alone, the incidence of hospitalized rhabdomyolysis was rather low. It is increased for fibrates, but it was low in the cases for gemfibrozil, low cases for fenofibrate. And then we see higher rates for fibrate and statin combination. However, they are based on very few cases.

This is the i3 study, i3 study number 2, that was conducted as a part of the postmarketing requirement.

This is to summarize the objectives of the study, calculated hospitalized rhabdomyolysis cases during use of statins, fenofibrate, and gemfibrozil monotherapy, concomitant use of statins and

fibrates, and periods of non-use. Non-use means no lipid-lowering drug use.

I used the proprietary Normative Health Informatics database, which is based on 44 major markets or health plans. It has medical and pharmacy data for more than 60 million current and past members between '93 and 2009. And at any given time here, in January 2006, there are 11 million current members, which represent about 3 to 4 percent of the U.S. population.

The population over 65 is somewhat underrepresented, as it is only 8 percent of the database versus 12 percent of the U.S. population. The average length of membership is 18 months, and it is possible to access medical records.

This is the study design. It is a retrospective cohort study, and it was explained as a new user design, a study period from '98 to 2008. Inclusion criteria were a minimum age of 17 years, commercial insurance coverage with medical and pharmacy benefits, and 183 days of continuous enrollment, at least. Also, patients had to have

at least one dispensing of a statin or a fibrate and were excluded if they ever received cerivastatin or clofibrate, or if they had a claims-based diagnosis of rhabdomyolysis during baseline. Exposure was ascertained based on the first prescription of a fibrate, or statin, or both. That was preceded by 183 days without a drug in the same class. During follow-up, each day was categorized by current exposure to statin and/or fibrate. Exposure duration was based on current days of supply plus 20 percent.

This is to illustrate how exposure was defined. This is a hypothetical patient, a single patient who started fenofibrate, continued fenofibrate, added lovastatin, and then switched from lovastatin to atorvastatin. And this is only a hypothetical example. Now, the index drug is the first drug that was preceded by 183 days without the drug. So in this very case, it would be lovastatin because fenofibrate is not preceded by 183 days. So the index drug is lovastatin, and this is where follow-up of this patient would

start.

Now, current exposure -- I would like to add this. The criterion that the exposure is padded by current days of supply plus 20 percent would close those minor gaps between prescriptions.

This is how follow-up would be categorized, so there is a baseline period and a follow-up period. And current exposure during the follow-up period in this case would be fenofibrate and statin, so the user is a combination user initially, and then we have a period of statin use only. Please note that the user would be considered a statin initiator, but early follow-up would be combination use.

Patients are followed up into a hospitalized case of rhabdomyolysis, or disenrollment, or end of the study, or double dispensing, where double dispensing is two statins or two fibrates on the same day.

To illustrate what no use is, no use is a period of no lipid-lowering drug use, and this period is preceded by some period of lipid-lowering

drug use because the inclusion criteria of the study requires that follow-up starts when a prescription is given.

These are the outcomes. The outcome is hospitalized rhabdomyolysis, and there was a three-step process to ascertain the outcome. The first step is a claim search, where the first or second position of inpatient claims was searched for any of these ICD-9-CM codes.

Other potential cases identified in this step; there was a claims profile review by a clinical consultant blinded to exposure, and they excluded obvious false positives. Unfortunately, we don't have much information about this step, what the criteria were.

The final step is a medical record review of patients who survived into this step. This was done by blinded clinical consultants and they used this criteria to ascertain whether the case was hospitalized rhabdomyolysis. There had to be a creatinine kinase increase more than 10 times the upper limit of normal with concomitant muscle

symptoms and no obvious acute alternated etiology. In addition, as was already discussed by Dr. Cooper in his question, there was a requirement of renal insufficiency, or renal failure, or creatinine elevation above the upper limit of normal. And, of course, it required hospitalization.

Now, the second requirement, renal involvement, selects only the very severe cases of hospitalized rhabdomyolysis. In fact, it narrows the case count that we would get. In one study that looked at hospitalized rhabdomyolysis cases found that only 33 to 51 percent of hospitalized rhabdomyolysis cases had acute renal failure. So this requirement would miss cases that don't have renal failure or renal insufficiency.

The investigators calculated incidence rates, which are confirmed cases of rhabdomyolysis divided by person years of exposure. And they calculated crude and adjusted incidence rate ratios. For the adjustment, all these variables were considered in the model, but not all of them were included in the final model due to statistical

considerations.

These are the results. About 1.1 million subjects initiated either statin, fibrate, or both. Majority initiated statin, and only .5 percent initiated both, but please understand that initiating both means the first statin and the first fibrate prescription on the same day, and none of them before.

This is based on initiation, not based on follow-up. We have 2.4 million years of follow-up. Current exposure was almost half statin monotherapy, almost 5 percent fibrate monotherapy, about 3 percent combination therapy, and about 45 percent periods of no lipid-lowering drug use.

For cases of severe hospitalized rhabdomyolysis, claims data review found about 2300 cases, potential cases, in 2171 patients. Seventy-five percent of them were selected for medical record review. That means about 900 did not pass the first step of claims data review. Of the medical records selected for review, 76 percent were obtained. So for 290 patients, no medical

records were obtained. And finally, 70 cases, or 7.4 percent, of the medical records obtained are confirmed cases for severe hospitalized rhabdomyolysis.

Four of these confirmed cases died within one day to six months of case diagnosis, but neither exposure information nor causes of death were provided to us, so we don't know whether rhabdomyolysis was underlying.

These are the sample characteristics, which were provided to us by drug-initiated. And that is the reason why we don't see no use, because patients cannot initiate no use based on the study criteria.

These are the numbers I presented before. About 87 percent of patients initiated a statin, 13 percent initiated a fibrate, and about .5 percent initiated both.

Statin uses were older, with a higher proportion older than 70. More fibrate initiators and combination initiators were male. Combination initiators had a higher proportion of

hospitalizations during baseline. That's the 183 baseline period. They had more prescriptions dispensed during this period. More of them were overweight or obese. More of them had diabetes. More had chronic ischemic heart disease, angina pectoris, or acute myocardial infarction.

These are incidence rates for severe hospitalized rhabdomyolysis. During periods of no lipid-lowering drug use, 24 cases were counted, which results in an incidence rate of 2.24 per 100,000 person years for follow-up. Statin users or period of statin use were associated with only a slightly higher rate, 2.46. We see an elevation of users of fenofibrate monotherapy and gemfibrozil monotherapy. Now, this is also during periods of use. This is not by drug initiated, so this is during follow-up.

Periods of follow-up on statin and fenofibrate had an incidence of about 12 per 100,000 person years and statin and gemfibrozil, about 38. Please note that the confidence intervals are fairly wide because the case counts

are still low.

These are crude and adjusted incidence rate ratios compared to statin only, and we see about a twofold increase with fenofibrate monotherapy, not statistically significant. We see about a 40 percent increase with gemfibrozil monotherapy, not statistically significant. We see a tripling of risk with statin and fenofibrate combination therapy compared to statin only, and the risk for hospitalized rhabdomyolysis with statin and gemfibrozil combination therapy is about 12 times increased. Both of the combination therapies have a statistically significant increase beyond statin monotherapy, but the confidence intervals between both combinations overlap.

Please note that differences between crude and adjusted incidence rate ratios are not as pronounced when we look at monotherapy, as when we look at combination therapy, which suggests that combination users have a higher baseline risk for hospitalized rhabdomyolysis before adjustment.

To compare study results between the Graham

study and the i3 report, which is the i3 study number 2, this combines both fibrates, fenofibrate and gemfibrozil, and these estimates are crude estimates. They go in a similar direction, so we see an increased risk for fibrate monotherapy in the Graham study, and also an increase, not statistically significant, in the i3 study, and a higher increase with combination therapy.

If we look at the absolute rates, the incidence rates, they are higher in the Graham study and that corresponds to the data that Dr. Kelly presented, and they are not as high as the i3 report. And this might be due to the stricter case definition that was applied in the i3 study.

Please note that case counts in the Graham study are very small. The resulting confidence intervals are wide. So it is possible the differences between the i3 study and the Graham study in the incidence rate ratio are due to random error.

These are all relative differences. Now, I

present absolute differences. The attributable risk of fenofibrate plus statin combination therapy compared to statin monotherapy is 5.6 additional cases per 100,000 years of exposure. And that means additional cases compared to statin monotherapy.

The resulting number needed to harm is, as presented before, almost 18,000. And that means 18,000 persons have to be exposed for one year to combination therapy to observe one additional case of severe hospitalized rhabdomyolysis.

That was for fenofibrate and statin. I have the same data for gemfibrozil and statin. Here, the attributable risk is almost 27, the number needed to harm, 3700 -- 3700 person years of combination exposure to observe one additional case. Please note here also, although the estimates are very different, confidence intervals do overlap.

The study has several strengths. One is its size, 2.4 million person years for follow-up and 70 confirmed cases, and also the medical record review

that validated the cases to eliminate false positives.

Unfortunately, the study also has some limitations. We found it's not an actual new user design because part of follow-up could be continued use, especially in monotherapy. The problem here is depletion of susceptibles. That means continuing users already show that they have sufficient efficacy and tolerable side effects, so they might be different from new users. In this case, it was mostly applied to monotherapy, so it would actually be conservative.

Also, outcomes were compared based on current exposure, which is good, but baseline characteristics were provided by initiated drug. So we don't really know how cohorts, based on current exposure, which were ultimately compared, differ based on their clinical characteristics. And you saw that in the demographics table that I showed you. There is no non-use cohorts, so we don't know how they actually look like.

Another example here is that almost

3 percent of person-time occurred during combination therapy, but only .5 percent of patients were initiators, and we don't know whether the characteristics of initiators match characteristics of current use of combination therapy. To illustrate, a person who initiated both drugs on the same day may differ from a person who has been using a statin and then initiates a fibrate. Concern here is we cannot evaluate the difference of cohorts, and thus multivariate adjustment.

The selected database somewhat underrepresented the elderly, who are at higher risk for rhabdomyolysis, and the concern here is that incidence rates and the attributable risk could be underestimated. Also, there is the potential for misclassification of exposure, especially in the no-exposure cohort. And that was found in the Graham study where they saw -- when they looked at medical records for patients that they classified as unexposed based on claims data, they found evidence of exposure in the medical

records. So it's possible that patients that were classified as unexposed are actually exposed, which might in part explain why the rate of hospitalized rhabdomyolysis for statins was very similar to non-use, which is not what you would expect.

Statistical adjustment changed incidence rate ratios significantly, especially in combination use, such as in the presence of confounding before adjustment. And, of course, it's unclear whether adjustment was sufficient.

Some risk factors for hospitalized rhabdomyolysis, including alcohol use, strenuous physical activity, and BMI, were not included in the analysis, which could potentially result in residual confounding. Other potential cases were missing medical records. Those were 24. That 24 percent were treated as non-cases, and this would also result in an underestimate of absolute risks.

Next, the case definition requiring renal impairment only selected the most severe cases of hospitalized rhabdomyolysis. And as was suggested

by the sponsor earlier today, this may not impact relative risks if the missing cases -- I call them missing cases; I know they are not missing but it's a question of definition -- if the cases that were not included are missing equally, based on exposure between both exposure cohorts, that should not affect the relative risk, but it would affect the absolute risk, and the risk difference, and the number needed to harm.

The study was underpowered to investigate specific drugs and doses.

Finally, I present the i3 study number 1, which was conducted earlier and included additional outcomes. Methodology is essentially the same. It was conducted in the same database. The study period was shorter, from 2004 to 2007 only. It did not include an unexposed cohort, and it had additional safety outcomes beyond rhabdomyolysis. These included myopathy, renal impairment, hepatic injury, and pancreatitis. And for some of the outcomes, models were adjusted for biliary disease.

These are the results for renal impairment,

and we see a slight elevation with fibrate monotherapy and with combination therapy. However, the elevation does not increase with combination therapy, so there is no evidence for an interaction here.

This is overall renal impairment. When we look at renal failure requiring renal replacement, we don't see any signal here, but the case counts are very low here. Please note that all of the cases in this table were included in a previous table as well.

For hepatic injury, we see point estimates above 1, suggesting the possibility of an increased risk. However, the case counts are very low, so it may not be statistically significant.

For pancreatitis, we see an increase with fenofibrate monotherapy, and for statin and fenofibrate combination therapy, statistically significant. You also see an increase with gemfibrozil, mono and combination therapy, but not statistically significant. However, this might be due to confounding by indication, as the study did

not adjust for baseline triglyceride levels. And elevated TG is a risk factor for pancreatitis.

To summarize, observational data suggests and increased risk for hospitalized rhabdomyolysis with statin and fibrate combination therapy versus statin monotherapy. On a relative scale, the increase is moderate to large with incidence rate ratios of 3 for fenofibrate and almost 12 for gemfibrozil. But on an absolute scale, the increase is small. You see 5.6 additional cases per 100,000 person years with fenofibrate, resulting in a number needed to harm of 18,000. And we see 27 additional cases per 100,000 person years with gemfibrozil, resulting in a number needed to harm of 3700.

We saw an increased risk of renal impairment associated with the use of fibrates and pancreatitis associated with the use of fenofibrate compared to statin monotherapy, but this increase was not further heightened when combined with statins.

The success of statistical adjustment is

potentially limited by small case numbers and the lack of information on some important risk factors. It is possible that residual confounding led to overestimated incidence rate ratios associated with combination therapy, as well as missed cases and rhabdomyolysis case definition requiring renal impairment, and, thus, only selecting the most severe cases could have underestimated incidence rates and attributable risk and overestimated the number needed to harm.

That concludes my presentation. Thank you.

DR. GOLDFINE: Thank you very much. We'll have our third FDA speaker.

FDA Presentation – Iffat Chowdhury

DR. CHOWDHURY: Good afternoon, Chairman Goldfine and members of the panel. My name is Iffat Chowdhury, and I will be presenting statin fenofibrate combination therapy after the ACCORD Lipid trial. My goal is to present the history of the fibrates and to provide a perspective on the results of the ACCORD Lipid trial as we attempt to define the regulatory approach to statin

fenofibrate combination therapy.

I will begin with a short description of the fibrate characteristics, then I will highlight results from the major fibrate cardiovascular outcomes trials. Next, I will present the efficacy and safety results from the pivotal trials that supported the Trilipix new drug NDA. I will present briefly the ACCORD Lipid trial results and follow with subgroup analyses from major fibrate studies.

As you heard earlier, fibrates are synthetic PPAR-alpha agonists. PPAR-alpha belongs to a subfamily of nuclear receptors which increase lipoprotein lipase and decrease Apo-C3, and thereby reduce triglycerides. PPAR-alpha activation also increases Apo A-1 and A-2 to ultimately increase HDLC.

In general, fibrates reduced triglycerides by 20 to 50 percent, increase HDL by 10 to 35 percent, and have variable effects on LDL, depending on the underlying lipid disorder. In terms of safety, as you heard from Dr. Hampp,

fibrates are associated with an increased risk of myopathy. Another well-known adverse effect of fibrates is cholelithiasis and cholecystectomy, due to the increases in biliary cholesterol concentration. Fenofibrate may also increase the risk for pancreatitis and venous thrombosis.

The earliest fibrate cardiovascular outcomes trials were conducted with clofibrate, which you see is in the upper left. Gemfibrozil was approved in the U.S. in 1981. Note that gemfibrozil is a non-halogenated fibrate, which chemically differentiates it from the other fibrates. Fenofibrate is a closely-related analog of clofibrate, and it was approved in the U.S. in 1993. Bezafibrate is not approved in the U.S., but I will be discussing data from a cardiovascular outcomes trial with this drug.

Trilipix is the choline salt of fenofibric acid. Trilipix disassociates in the gastrointestinal tract to form fenofibric acid, the active ingredient for Trilipix. Fenofibrate is also converted to fenofibric acid. Thus, both

fenofibrate and Trilipix share the same active ingredient.

Moving onto the fibrate cardiovascular outcomes trials, this slide provides a timeline for the major fibrate cardiovascular outcomes trials. Over the past 40 years, fibrate trials have produced mixed results in terms of cardiovascular efficacy and overall safety. The trials with clofibrate raise concern about a lack of cardiovascular benefit and possible increase in total mortality.

As I will discuss in greater detail, trials with gemfibrozil were favorable and restored clinical confidence, at least with this particular fibrate. I would point out that all of these trials, with the exception of the ACCORD Lipid trial, were with fibrate monotherapy.

This slide summarizes the four trials that I will discuss in some detail. Two involve gemfibrozil, one bezafibrate, and one fenofibrate. The Helsinki Heart Study was a double-blind, randomized, control trial evaluating the long-term

safety and efficacy of gemfibrozil, 600 milligrams, twice daily, versus placebo. 4,081 men between the ages of 40 and 55 years, and free of coronary heart disease were enrolled. The inclusion criteria was a non-HDLC greater than or equal to 200 milligrams per deciliter. The primary endpoint was fatal and non-fatal myocardial infarction and cardiac death.

Approximately 3 percent of the study population had type 2 diabetes. The study was composed entirely of men and the baseline lipids are listed on the slide. Relative to placebo, those patients in the gemfibrozil treatment group had an 8 percent reduction in LDL and a 10 percent increase in HDL. Triglycerides decreased by 35 percent and non-HDLC increased by 12 percent. After five years, there was a significant reduction in the relative risk for fatal and non-fatal MI and cardiac death in the gemfibrozil-treated group.

Another randomized placebo control trial using gemfibrozil was a Veterans Affairs High Density Lipoprotein Cholesterol Intervention trial, or VA-HIT. 2,531 men with documented coronary

heart disease, and HDL less than or equal to 40, LDL less than or equal to 140, and triglycerides less than or equal to 300 were enrolled in this trial. The primary endpoint was a combined incidence of non-fatal MI or death from coronary heart disease.

Patients with type 2 diabetes made up approximately 25 percent of the study population. The study only included men, and the mean age was 64 years. Mean baseline lipids are as shown here. Of note, the mean baseline level of HDL in this trial was 32.

Relative to placebo, gemfibrozil treatment decreased triglycerides by 31 percent, increased HDL by 6 percent, and did not change levels of LDL. Gemfibrozil was associated with a significant reduction in the relative risk for the composite endpoint of death from coronary heart disease or non-fatal MI.

One year after the VA-HIT trial, the results of the bezafibrate infarction prevention, or BIP trial, were reported. The BIP study was a six-year

randomized control trial of bezafibrate, 400 milligrams daily versus placebo.

As I mentioned earlier, bezafibrate is not approved in the U.S. 3,090 men and women with coronary artery disease and not on any lipid-lowering medication were studied. To be included in the study, participants had to have a triglyceride less than or equal to 300, HDL less than or equal to 45, and LDL less than or equal to 180. The primary endpoint of the study was fatal MI, non-fatal MI, or sudden death.

Approximately 10 percent of the study population had type 2 diabetes. Unlike the two previous trials, there were some women enrolled in BIP. However, they comprised only 10 percent of the study population. The mean age was 60 years and the mean baseline lipids are as listed on the slide.

Compared to placebo, bezafibrate dramatically increased HDL by 18 percent, decreased LDL by 7 percent, and triglycerides by 21 percent. However, at the end of six years, there was no

significant difference between the bezafibrate and placebo groups in the risk for non-fatal MI, fatal MI, and sudden death.

The fourth trial I want to discuss is the Fenofibrate Intervention and Event Lowering in Diabetes, or the FIELD study. This was a five-year randomized placebo control trial of fenofibrate, 200 milligrams daily. 9,795 men and women who are not receiving statin or any other lipid-lowering therapy at study entry were enrolled.

Inclusion criteria were a total cholesterol level between 116 and 250, plus either a triglyceride concentration between 89 to 442 milligrams per deciliter or a total cholesterol to HDL ratio greater than or equal to four. The primary endpoint was the first occurrence of either non-fatal MI or death from coronary heart disease.

All participants in the FIELD trial had type 2 diabetes, and the median hemoglobin A1C was 6.9 percent. The mean age was 62 years, and women comprised 37 percent of the population, making this the only fibrate trial with a sufficient number of

women to examine results by gender. Approximately 22 percent of participants had cardiovascular disease. Mean baseline lipids are as shown on the slide.

Relative to placebo, fenofibrate treatment decreased LDL by 6 percent, triglycerides by 22 percent, and increased HDL by 1 percent. Like the results from the BIP trial, there was no significant difference between the fenofibrate and placebo groups in the risk for non-fatal MI and coronary heart disease death.

Since Trilipix is the focus of today's meeting, and since Trilipix and fenofibrate have the same active ingredient, fenofibric acid, I want to mention some of the safety findings from the FIELD trial. Rhabdomyolysis was reported in three subjects on fenofibrate as compared to one subject on placebo. There are a greater number of events of pancreatitis and venous thrombosis on fenofibrate than on placebo. And 2 percent of subjects on fenofibrate as compared to 1 percent on placebo had serum creatinine concentrations greater

than 2.2 milligrams per deciliter.

To summarize, we have favorable or positive cardiovascular outcomes data with gemfibrozil in two clinical trials that only included men. The cardiovascular outcomes data with bezafibrate in BIP and fenofibrate in FIELD are, strictly speaking, negative, although one could say that the primary results did at least lean in the right direction.

I want to now move on to discuss some aspects of the Trilipix new drug application. As another reminder, fenofibric acid is the active ingredient of fenofibrate and Trilipix. Three similarly designed 12-week clinical trials were conducted in support of the Trilipix NDA. Each trial had six treatment arms, one treatment arm for fenofibric acid monotherapy, three treatment arms of statin monotherapy, including a low-dose, a moderate-dose and a high-dose statin, and two treatment arms of combination fenofibric acid plus statin.

The combination treatments were only with

the low-dose and moderate-dose statin. 2,698 men and women were enrolled in these trials.

The inclusion criteria for the 12-week trials were a triglyceride concentration greater than or equal to 150, HDL less than 40 or 50 for men and women, respectively, and LDL greater than or equal to 130. Twenty-two percent of the study population had type 2 diabetes, 52 percent were women, and the mean age of the study population was 55 years.

There were three primary endpoints in the Trilipix pivotal trials: triglycerides, HDL, and LDL. For triglycerides and HDL, the primary comparison groups were fenofibric acid plus statin compared to statin monotherapy. For LDL, the primary comparison groups were fenofibric acid plus statin compared to fenofibric acid monotherapy.

This slide shows the lipid changes after 12 weeks of treatment. The combinations of fenofibric acid plus low-dose statin and moderate-dose statin significantly improved HDL compared to the corresponding doses of statin monotherapy.

Similarly, the combination of fenofibric acid plus low-dose statin and moderate-dose statin significantly increase triglycerides to a greater extent, compared to the corresponding dose of statin monotherapy.

The combination of fenofibric acid plus a low- or moderate-dose statin significantly reduced LDL compared to fenofibric acid monotherapy. Taking a closer examination of the LDL changes, you can see that the addition of fenofibric acid to low- or moderate-dose statins resulted in a slight reduction in LDL. However, the largest numerical reduction in LDL was achieved with high-dose statin monotherapy.

During the 12 weeks of the pivotal trial, there were no cases of rhabdomyolysis reported in any treatment group. There was one case of pancreatitis in a patient receiving fenofibric acid plus a statin, and two patients, both on fenofibric acid monotherapy, reported venous thrombosis.

Based on favorable changes in HDL and triglyceride levels, and a favorable safety

profile, Trilipix was approved in 2008. In addition to the standard fenofibrate indications, Trilipix was granted an indication for coadministration with a statin. The exact wording is shown here on the slide. "The language used for this indication is consistent with the recommendations made in NCEP-ATP III treatment guidelines." The labeling for Trilipix also includes this limitation of use statement.

You've already heard a lot about the ACCORD trial today, so I'm not going to spend very much time on this study. However, I do want to spend a few minutes discussing a couple of aspects of the trial. This is not a criticism of the trial, but the ACCORD Lipid study was not designed to answer the question of whether the fenofibrate reduces the risk of major cardiovascular events in patients on a statin at LDL goal, but with elevated triglycerides, with or without low HDL.

For example, subjects with triglycerides less than 200 were enrolled in the study. In addition, following four weeks of open-label

simvastatin therapy, subjects were started on fenofibrate or placebo regardless of their triglyceride or HDL levels.

In terms of safety, in the ACCORD Lipid study, there were four cases of myopathy in the fenofibrate arm versus three in the placebo arm. There were five reported cases of pancreatitis in the fenofibrate group compared with four in the placebo group. There were no venous thrombosis events reported in the trial.

As you heard earlier from Dr. Ginsberg, more subjects randomized to fenofibrate versus placebo had increases in serum creatinine during the study. In addition, a greater number of subjects in the fenofibrate group had their dose of study drug reduced or had study drug withdrawn due to a low estimated GFR or elevated serum creatinine. The clinical significance of these findings is unclear. However, at this time, fenofibrate does not appear to be a nephrotoxic drug.

I'd like to finish my presentation with a comparison of the major subgroup findings from the

ACCORD Lipid trial with subgroup findings from the fibrate trials I presented earlier. As a reminder, the overall results from the ACCORD Lipid trial show that there was a non-significant reduction in the risk for major cardiovascular events in the fenofibrate group.

This table shows the two subgroups of interest out of 23 subgroups examined in the ACCORD Lipid trial. While the point estimate of the hazard ratio for the primary outcome was favorable in men, 0.82, the point estimate of the hazard ratio was unfavorable in women. The interaction p value indicates that the treatment effects were statistically significantly different in men versus women.

In the second subgroup of interest, the point estimate of the hazard ratio for the primary outcome was favorable for subjects with an HDL less than or equal to 34 and triglycerides greater than or equal to 204, compared to all others. The interaction p value was 0.06.

A logical response to observing these

findings is to see if similar findings were noted in previous fibrate trials, in particular the FIELD trial, as this is the only other outcomes trial with fenofibrate and one that enrolled a sufficient number of women to examine results by gender.

But before I do, I will discuss subgroup analyses from the previous fibrate trials. These subgroup analyses are based on data provided in the original or the primary publication. The analyses are conducted either with the primary endpoint or in some cases with a secondary endpoint. The interaction p values, I will show you, were not reported in the initial study reports for the BIP trial or the VA-HIT trial. FDA statisticians calculated those values.

In the VA-HIT trial, in which the primary outcome was positive, subgroup analyses were reported for a secondary outcome. There was no evidence of differential treatment effects in subjects with HDL levels above or below 31.5 milligrams per deciliter. Likewise, there was no evidence of differential treatment in subjects

with baseline triglycerides above or below 151 milligrams per deciliter.

In the BIP trial, which you will recall was a negative study, subgroup analyses were provided for the primary endpoint. This slide shows two out of the numerous comparisons provided in the original publication of the trial.

As you can see, the treatment effects were similar in subjects with baseline HDL less than 35 and triglycerides greater than or equal to 150, compared with all others. The treatment effects were numerically greater in the subjects with baseline HDL less than 35 and greater than or equal to 200, compared with all others. The interaction p value was 0.05.

Finally, the FIELD study. You will recall that this study had an overall negative result. These subgroup analyses are with the secondary endpoints. The treatment effects were not significantly different in subjects with low HDL and high triglycerides. The interaction p value is 0.6. In the gender subgroup, while the treatment

effect was numerically greater in women versus men, the difference between treatment effects was not statistically significant. The interaction p value is 0.3.

To summarize, the fibrate monotherapy cardiovascular outcomes trials have produced mixed results. Trials with gemfibrozil have been positive, whereas trials with bezafibrate and fenofibrate have been negative. It is unclear if the differences in trial outcomes are due to pharmacodynamic differences between the individual fibrates, the population studied, both, and/or other factors.

The approval for the Trilipix coadministration with a statin indication was based on favorable changes in HDL and triglycerides, compared with statin monotherapy. In the ACCORD Lipid trial, fenofibrate plus a statin, as compared to statin monotherapy, resulted in an essentially negative outcome.

The overall findings from the ACCORD Lipid trial do not, as the authors of the study

acknowledge, support the routine use of combination therapy with fenofibrate and simvastatin to reduce cardiovascular risk in the majority of high-risk patients with type 2 diabetes.

There was a subgroup finding suggestive of harm in women treated with fenofibrate in the ACCORD Lipid trial. This finding was not observed in the FIELD trial, and there does not appear to be a biologically plausible explanation for the results.

There was a subgroup finding suggestive of greater benefit in the population with baseline triglycerides greater than or equal to 204 and HDL less than or equal to 34, compared with all others. Some post hoc subgroup analyses of fibrate monotherapy cardiovascular trials raise the possibility that patients with triglycerides greater than 200 and HDLs below 35 may derive benefit with fibrate therapy.

To conclude, I would like to quote the investigators of the ACCORD Lipid study. The results of the ACCORD Lipid subgroup analysis,

together with those previous fibrate trials, support the hypothesis that fibrate therapy may reduce cardiovascular events among patients with clinically significant dyslipidemia. On this point, I would agree with the investigators that this is a reasonable interpretation of the available data.

The investigators of the ACCORD Lipid trial have also remarked that a definitive clinical trial involving persons with high triglycerides and low HDL would provide critical information regarding this issue. I certainly agree with this statement and would add that a trial would also provide critical information regarding the treatment effect of fenofibrate plus a statin in women versus men.

Clarifying Questions from Committee to FDA

DR. GOLDFINE: Thank you very much for that clear presentation.

I believe we're going to open to questions, and I'm going to start with Dr. Heckbert, who actually had her question cut off before lunch.

DR. HECKBERT: Great. Thank you.

My question was to Dr. Colman or any of the other FDA presenters. And it regards that third indication that we're here to discuss today.

So as you know, the FDA has faced a number of situations with drugs that were approved on the basis of their effects on surrogate endpoints, where after trials were done where cardiovascular outcomes were used as endpoints, it was found that there are a few drugs that had adverse outcomes that weren't initially anticipated.

In view of that, and because we're here today to review that third indication about combination therapy with statin and Trilipix, my question is, what does the FDA currently, today, consider the level of evidence required to write an indication? So the level for a lipid-lowering drug, particularly a lipid-lowering drug that's going to be used as add-on therapy to statins, which have been proved in long-term trials with clinical endpoints.

DR. COLMAN: That's an evolving area. We've been somewhat lucky in that the approval of the

original statins was based simply on the fact that they lowered LDL, and people at that point believed that LDL was a valid surrogate for CV risk reduction. It turned out that that certainly does seem to be the case, certainly with statins.

We have grown certainly more leery of drugs that work by increasing HDL following the torcetrapib experience. As you know, there are two newer CTP inhibitors that are currently being studied in very large cardiovascular outcomes trials. So we are certainly not going to entertain approving a CTP inhibitor without outcomes data that are favorable and in front of us.

We're faced with this quandary today. When Abbott came to us with this application back in early 2008, it was clear at that point that most people realized that statins were first-line therapy for just about every different lipid disorder. And based on the fact that the NCEP-ATP III guidelines mention that it was a reasonable option if you have someone on a statin and they're at goal, but they have elevated TG, that you

consider treating them with a fibrate. Certainly, the lipid numbers go in the appropriate direction. That wasn't based on trial data. We knew that the ACCORD Lipid study was ongoing at that time. So we made a judgment.

We did make quite a few changes to the indication language. When Abbott first proposed the label, it was very open-ended and very broad. And we said, no, we're going to try to streamline this so that it would be appropriate for people who were on a statin, at goal, and then only if they need TG lowering or HDL raising, that this might be appropriate.

So if it's strictly an LDL-lowering drug and we don't have any known safety issues, we'd certainly be more comfortable approving that without outcomes data. I think when we start talking about HDL and triglycerides, we have a greater sense of unease about whether we should approve those products simply based on changes in HDL and triglycerides, rather than saying, you're going to have to show us favorable outcomes data.

DR. GOLDFINE: Thank you.

Dr. Hiatt?

DR. HIATT: I'm curious what the FDA thinks about this issue of prior statin use and your analysis of that. It strikes me as it's a confounding issue. In other words, it was associated with the exposure, at least in some patients, and certainly, it seems to influence the outcome.

So my first question is, do you agree with that? Did you look at it? What conclusions did you draw? And then I guess the thing that I'm more concerned about the prior statin use is that it is a marker of other unmeasured confounders that might have actually driven the results in a positive direction due to other features of patients who were requiring statin use before they were entered into this trial versus those who were not. Obviously, the absolute risks were higher.

So I'm wondering what other, perhaps, concerning unmeasured confounders, could have associated with that particular clinical marker.

DR. CHOWDHURY: I agree with you that primary baseline statin use could be a confounder. Overall, the ACCORD Lipid trial was not designed to answer what we were really asking, what the clinicians needed to know. So all of these factors, unknowns, could bias the result.

DR. HIATT: So statistically, was prior statin use confounding, yes or no?

DR. COLMAN: I don't think we have that answer. I'm looking at my statisticians.

DR. HIATT: I guess I'd open that up to the sponsor, too, if that's appropriate.

DR. GOLDFINE: Does anybody in the sponsor -- I see a lot of heads shaking no. Does the sponsor want --

Thank you. Please make sure you just address the one question at hand.

DR. KOCH: Gary Koch, Biostatistics Department, University of North Carolina. My activity for Abbott is through an agreement with my university that provides funds for part of my salary and travel expenses.

Prior statin use, as far as I can tell, is a baseline characteristic, and as a baseline characteristic, patients would be randomized equally to the two arms. And so it should not be a confounder. And as far as I know, it isn't a confounder because no interaction was necessarily reported for it in the sense of the overall trial results. There is a suggestion that it has a role within the dyslipidemic subgroup.

DR. GOLDFINE: Dr. Kaul?

DR. KAUL: Yes. In slide 42, you asserted that the results of the ACCORD Lipid subgroup analysis support the hypothesis. Just a clarification, support as in validating or support as in raising?

DR. COLMAN: If I could speak for Iffat, which I think she'll probably let me do. Right?

[Laughter.]

DR. COLMAN: These are actually the words from Dr. Ginsberg and his colleagues.

DR. KAUL: But she said she agrees with that.

DR. COLMAN: Right. And I agree with them, frankly. I think the key words here -- and I think Dr. Ginsberg and his colleagues chose these words very carefully -- first of all, he says, "support the hypothesis," so "hypothesis" is still the main word that's being thrown around here, even though you have three or four previous trials that show greater numerical benefit in the subgroup with high TG, low HDL. Second of all, he says may reduce cardiovascular events.

So I see this as an appropriate hedge on the available data. I think this is an appropriate interpretation.

DR. KAUL: The reason why I ask is because she appropriately emphasized that, depending on how you do the cutpoints for the triglycerides and the HDL, you get different results. And so the point I'm trying to make here is that we should not allow ourselves to be fooled by randomness, by invoking biological plausibility, which is every trialist's favorite mistress.

So I think it makes sense, but we have

missed four opportunities to validate this hypothesis, which was just raised in the Helsinki Heart Study. We missed that in the VA-HIT study. We missed it in the BIP study. We missed it in the FIELD study. And we missed it in the ACCORD study.

DR. COLMAN: That's why we have our first question for you.

[Laughter.]

DR. GOLDFINE: Dr. Ginsberg?

DR. GINSBERG: Since my name is listed under those words -- they're listed because I was the first author on that reference, obviously. This comment followed the conclusion that our results indicated it wasn't appropriate to treat the majority of patients with a fibrate on top of a statin to reduce cardiovascular risk.

This statement was vetted not only by the ACCORD steering committee but by the New England Journal of Medicine editorial staff. But having said that, I think, as Dr. Colman just said, to our minds, it's further support for a hypothesis that's been out there. It's further support because it,

in a subgroup analysis, directly tested what post hoc analyses of monotherapy trials had suggested, that there was something about people with high TG and low HDL that made them respond potentially better to fibrate.

The wording is -- I think "hedge" is the right word, and it's an appropriate hedge because of all the caveats you've raised.

DR. GOLDFINE: Thank you.

Dr. Brittain?

DR. BRITTAIN: I don't know if this is for the FDA or the sponsor. But I guess I'm a little confused about some of the results presented for the previous studies. For example, in the FIELD trial, I believe the FDA presented results that showed that there did not appear to be a difference in the treatment effect by baseline lipid values, and I thought that the sponsor had presented something different from that.

So I wanted to see, are those in conflict or what?

DR. CHOWDHURY: The data I used is from the

original publication of the FIELD trial.

DR. BRITTAIN: But did the sponsor report different from that? Are you using a different triglyceride value in your report?

DR. GOLDFINE: Would you like to answer that?

DR. KELLY: The dyslipidemia subgroup from the FIELD study that we used in our analyses was a reported dyslipidemia subgroup from FIELD. It differed from the one that Dr. Chowdhury presented, but it was presented by the FIELD investigators as part of their analysis of the FIELD data. And Dr. Keech is here from the FIELD study and he can speak a little bit more about that.

DR. KEECH: Thank you and good afternoon. My name is Anthony Keech. I'm a professor of medicine, cardiology, and epidemiology at the NHMRC Clinical Trial Center in Sydney, Australia, and part of the University of Sydney. My conflicts are that Abbott has funded or reimbursed my trip here today. I've received honoraria from them, as well as most of the statin companies, for speaking. And

the Laboratoires Fournier, who are now part of the Abbott group, funded the FIELD study.

Both comments are true. Our original, pre-first patient randomized cutpoints for dyslipidemia were those that Abbott presented today. The triglycerides greater than 204 and low HDL presented as less than 40 for men and less than 50 for women.

During the course of the trial, whilst they continued to be blinded, the ATP III NCEP guidelines reduced the level of triglyceride that they recommended be targeted for treatment from 200 to 150 milligrams per deciliter. And the rationale for that, I understand, related to that being the point at which LDL particles tended to become small and dense.

The steering committee of the FIELD study agreed, at that point, to modify the definition of dyslipidemia as the primary analysis for that observation from the Helsinki Heart Study to the 150 milligram per deciliter level that was presented by the FDA moments ago. Both of these

analyses were reported in a paper in Diabetes Care in 2009.

Both groups, based on either of those definitions, were independently significant for reductions in total cardiovascular events. But the test for interaction against all others was only .052 for the marked dyslipidemia with the triglyceride level of 204, rather than the dyslipidemia of 150.

With adjustment for HBNC, age, and prior CVD history, any low HDL or any level of triglyceride along or together with low HDL was statistically significant overall in the study. And has been mentioned previously, in particular in women, the benefits of fenofibrate, albeit in monotherapy primarily in that study, were greater consistently across all the endpoints than in men.

DR. GOLDFINE: Thank you.

Dr. Hiatt?

DR. HIATT: I have a different question about the pancreatitis risk, a couple of concerns about that. In the trials themselves, patients

really weren't enrolled with extremely high triglyceride values, so I suppose we can't really know if lowering a very high triglyceride level would prevent an event as pancreatitis. But it does seem to be a numeric imbalance in pancreatitis in the drug group.

So my first question is to better understand that, do we know more about those cases? Is there some other mechanism going on? But I guess my bigger question is in the observational databases that you presented. In those situations, there probably were patients with more elevated triglycerides.

I'm just wondering if we can draw any conclusions about fibrate drug therapy and pancreatitis. Are we actually preventing cases or are we causing cases? And I raise the question because clinicians typically treat these numbers for one of two reasons. They want to prevent cardiovascular events, which we're discussing today, or they're fearful of pancreatitis, which is a very low-risk event. And whether we can learn

anything about whether that's actually occurring or not would be helpful.

DR. CHOWDHURY: I think I would say that when I was reviewing the safety aspects of the ACCORD Lipid trial, I found it rather difficult to do because the ACCORD Lipid was conducted in the manner of a large simple trial, and not all of the chemistries and laboratory values that you would have wanted were there.

For example, there were three cases of hepatitis, but only the ALT was reported. So it was hard to know what to make of that. And the case reports for the pancreatitis, per se, all of the case report forms were not made available to us until very late into the review, and they were not all there, only about 45 of the case report forms.

DR. HIATT: But you can conclude that there's a numeric imbalance in ACCORD?

DR. CHOWDHURY: Right. But I think what I'm trying to say is that with the ACCORD Lipid, we did miss the chance of really understanding the full safety profile of the combination treatment, and we

don't have that. I can't make it definitive.

DR. HIATT: So, Dr. Hampp, can you help us understand this increased risk that you presented for pancreatitis? Is that drug related? Or what do you think is going on?

DR. HAMPP: Unfortunately, since the study did not adjust for baseline triglycerides, you cannot make that call. You ask if that's possible that the drug increased or decreased pancreatitis. Both could be the case. In fact, it could be the case that both happen at the same time, that pancreatitis is decreased through decreased triglyceride and increased through some other mechanism. And the study is not able to answer that question.

DR. HIATT: So from what we've seen today, we can't really draw any conclusions about the risk of pancreatitis? I see that as an event, just like an MI, a stroke, or a death is an event. It's a very low-risk event, but I raise it because I think, as clinicians, we think about that as something that's added benefit to lowering

triglycerides. And I just want to understand, from what we heard today, which is probably not entirely fair because these studies weren't designed to answer that question -- the observational databases might enlighten us. We can't draw any conclusions, really, about whether there is a terribly increased risk or the drug is actually reducing that risk.

DR. GOLDFINE: I think that that's an observation that they can't answer, so Dr. Smith?

DR. SMITH: Following on Dr. Hiatt's comments, I have real concerns about the safety issues and how actual incidence were assessed. There are substantially greater flaws than were identified for us.

How does the FDA feel about the reliance of observational studies that draw on claims data? For instance, how about restricting oneself to commercial carriers? Does the FDA feel that the exposed population is so homogeneous that the non-commercial carrier-covered patient is identical to that of those with commercial healthcare coverage?

Any thoughts about this? Should I be

concerned?

The other aspect that I thought was striking had to do with one of the analyses, chart reviews, and 24, 25 percent of the charts were unrecoverable and were handled as non-cases.

Isn't that a pretty large fraction of those cases that raise some red flags?

DR. IYASU: So let me comment just in general about observational studies and how we assessed the validity of results that come out of observational studies. These are real-life experiences, and the databases that we use, typically for observational studies, have their own attributes in terms of what information is captured regarding exposures, regarding outcomes, and the validation.

They all have limitations in terms of, let's say, are the outcomes that we're using, or to identify outcomes, using ICD codes and if those ICD codes do validate what actually is happening in terms of outcomes. So we provide probably a higher quality of evidence threshold for outcomes that are

validated through medical records. But the medical records are just what you have as the ultimate set of gold standards for outcomes.

For exposures, that's also another -- there are many different ways of categorizing exposures in terms of what design you're using. So the data that comes from observational studies, no one study can confirm an association or exonerate a drug from a safety issue. This is a multiplicity of different study designs, different study databases that would give us greater level of comfort about how much comfort we draw from the data that comes up.

So it's really dependent on many aspects of the strengths and limitations of the data. So do they represent the homogeneous? Are they all homogeneous? Probably, the results have to be looked at in terms of the populations that are represented in the different databases.

You may find a negative study in one database and you may find a positive association in a different one, but we do take the attributes of

those databases, in terms of the exposure mapping, the outcome validation, and what formularies they may have in their patient population, if there is any selection bias, if there is any channeling. All those things have to be considered.

So I can't make a general statement, but we do take into consideration all those issues.

DR. GOLDFINE: Thank you.

Do you have an additional comment?

DR. HAMPP: I wanted to answer the second part of the question about the missing medical records.

The study missed 26 percent of the medical records, and although that's on the high side, it's not unusually high, but we would be more happier to see above 90 percent recovery rate. If the same confirmation rate was applied to the not included cases, as we saw in the included cases, we would have 22 more cases on top of the 70 cases. In the optimal case, the investigator would conduct a sensitivity analysis where they included all the cases that were potentially missed, assigned them

in the same proportion to exposed and non-exposed, and would provide estimates of how absolute risk would change.

If the missingness is not related to exposure, that means that the same rate of cases is missing in exposed as in unexposed, this would not change relative estimates, but it would change absolute estimates, absolute risk, risk difference, number needed to harm.

DR. GOLDFINE: Dr. Kaul, and then we will be coming back to the previous question.

DR. KAUL: Dr. Chowdhury, I was particularly struck by the fact that you did not present the pooled data for the fibrate trials, looking at the subgroups, the atherogenic phenotype. Why is that? You don't think they are informative? What is the FDA's position on that particular pooled subset analysis, or for that matter, the three meta-analyses that the sponsor quoted and cited?

DR. CHOWDHURY: Are you referring to the June analysis, the June meta-analysis?

DR. KAUL: Abbott did their own meta-

analysis, and in the June analysis, and then particularly the pooled estimate that they presented, slide number 31.

DR. CHOWDHURY: Well, this is just my particular opinion after reviewing the data, but I don't believe that all the fibrate trials can be pooled because there are differences between fibrates.

Gemfibrozil is a partial PPAR-alpha agonist, whereas fenofibrate is a full agonist of PPAR-alpha, and they have different pharmacokinetic characteristics. So that's open and the populations were very different. So that's one of the reasons why we didn't present.

DR. KAUL: You said your personal opinion. I asked the question, what is the FDA's position, because we have to consider these data. Are they informative on our judgment or are they misinformative?

DR. COLMAN: I frankly don't have an opinion one way or the other.

[Laughter.]

DR. GOLDFINE: Thank you. I think that's it.

[Laughter.]

DR. GOLDFINE: I have one question, and I am actually not sure whether this should be directed to the FDA or the sponsor, so I'll give the FDA the first pass.

I know that PPAR-alpha combination therapy has previously been under development and was stopped due to cardiovascular safety.

Is there any signal, since within the ACCORD a reasonable number of patients were on TZDs, that there was any drug interaction either with the TZD or any of the potential other therapies that were used in the trial? And if you can't, then perhaps the sponsor can address that.

[Pause.]

DR. GOLDFINE: We can also come back to that after the OPH.

Does the sponsor want to answer that question? Yes? Okay. And then perhaps you can go right into your additional comment on the Eye

findings.

DR. KELLY: As far as the question about any interaction data with thiazolidinediones, I discussed earlier that there were rare reports in our Trilipix clinical program in which paradoxical HDL decreases occurred. This also was observed in ACCORD Lipid at a low rate, and there was a protocol notification process that was implemented during ACCORD Lipid to manage any patients who were receiving concurrent rosiglitazone and had decreases in HDL observed.

There was central laboratory notification and management thereafter. There was first a confirmation, laboratory testing several months later, and then if the HDL was still low, then subsequently thereafter, modifications were made to the patient's treatment regimen. For the most part, those individuals had their rosiglitazone discontinued and continued on mass medication.

As far as the follow-up question, this was Dr. Kaul's question concerning the ACCORD Eye study. And we do have the vision loss follow-up

information. And if we could put that up on the screen, the slide that's on preview.

What we have in the first part is the progression of diabetic retinopathy, which was the primary endpoint for this study. And you see that after four years, at the 48-month mark, the rate of progression of diabetic retinopathy was 6.5 percent for the coadministration group with fenofibrate and simvastatin, versus 10.2 percent with simvastatin monotherapy.

But Dr. Kaul was asking about one of the many secondary endpoints from the study, which is moderate vision loss, and there was no difference between treatment groups for that secondary endpoint of moderate vision loss.

DR. KAUL: Can I ask a follow-up question, if it's all right?

Is this a typical or atypical scenario, where the surrogate goes in one direction and the clinical relevant endpoint doesn't go in the same direction?

DR. KELLY: Dr. Keech is an expert on

fenofibrate-related eye conditions, and he obviously conducted the FIELD Eye substudy. So I'm going to let Dr. Keech further comment on this particular correlation.

DR. KEECH: Thank you. As was indicated before lunch, the progression of ETDRS scores is a widely-used instrument to look at short-term changes in retinopathology in diabetes. The problem with visual acuity in these sorts of studies is that the majority of patients are not in a position to enjoy any improvement in visual acuity, where it starts normal.

So in both the ACCORD Lipid and the FIELD studies, the majority of patients had no retinopathy at baseline and didn't develop it during the study. For that reason, the fenofibrate can't improve what would be normal visual acuity.

To do the sort of study that you are looking for, you would need to take people with thickened macular -- central macular thickening would be required to generate abnormal visual acuity, which could then be improved by treatment such as studies

planned.

In fact, there's one ongoing at the moment in type 2 diabetes with fenofibrate involving 100 patients in Europe who all have a thickened central macular, based on OTC measurement. And that's the sort of study one needs to do to demonstrate an improvement in visual acuity with such treatment.

Certainly, the drug reduces macular edema, both in the clinical experiment of the FIELD study and the ACCORD study, where laser treatment in FIELD for macular edema was reduced by 30 percent, as it was for peripheral retinopathy, both with hugely significant p values. And in animal experiments, the capillary leakage seen in the retina in diabetes is dramatically reversed, both fenofibrate as well as all the inflammatory processes that underlie it.

So we think it's a valid question. It's just a different type of study you'd need to demonstrate a change in visual acuity, where the majority of patients don't have any retinopathy.

DR. GOLDFINE: Final question.

DR. KAUL: Would it be fair, then, to say that the ACCORD study was really not designed to draw any valid conclusions about microvascular outcomes, because of the renal profile, as well as because of their retinopathy profile; they were relatively less sick?

DR. KEECH: Well, it depends on what you mean. I think the ACCORD study is an excellent study to look at microvascular outcomes, but just not visual acuity. It's had an extraordinary benefit on ETDRS progression, a 40 percent reduction with fenofibrate treatment; FIELD, a 37 percent reduction, two studies showing exactly the same thing.

Both studies have demonstrated reductions in albuminuria. And in the FIELD study, not only was there less progression of albuminuria, but also regression of albuminuria in people with existing albuminuria at baseline who received fenofibrate.

In February of this year, in Diabetologia 2011, we reported not only the reduction of albuminuria, but renal preservation, preservation

of GFR. And you saw in the slide presented by the sponsor earlier, that at the end of five years in the subset of 660 patients, it came back for a further measurement eight weeks after study cessation that the creatinine increased sustained by fenofibrate during treatment, five years of treatment, reversed fully. And in fact there hadn't been a significant fall in GFR calculated from baseline to that timepoint, whereas 8 percent of renal function had been lost in the placebo group. This difference represented an 80 percent protection of renal function, or about 3.7 kidney years saved.

Just on the same question, I guess, the increase in creatinine was not associated with any less renal protection than overall. And the patients who had the greatest increase in creatinine actually had the greatest reduction in cardiovascular events in the study.

So it was overall significant, but a much larger absolute reduction in the group with the greatest creatinine increase. It may well be that

the creatinine increase is a marker of bioactivity, therefore, and we certainly don't think it's actually a primarily renal phenomenon.

DR. GOLDFINE: Thank you very much.

I believe we will now move onto the open -- absolutely.

DR. COLMAN: This is a question for Abbott.

Have you, at this point, or do you plan to in the near future, approach the appropriate FDA divisions to speak to them about getting indications specific to these microvascular complications?

DR. GOLDFINE: Can you repeat your question?

DR. COLMAN: Yes. We're obviously making a big deal out of the potential microvascular benefits of fenofibrate. I want to know, from a company standpoint, where you stand in terms of seeing these data and whether they are sufficient to go to the FDA to enter in dialogues about whether you could get specific indications for these endpoints.

DR. KELLY: As Dr. Keech mentioned, there's

currently an ongoing retinopathy study using Trilipix fenofibric acid in Europe. The results of those are going to be available later this month or early next month. We want to look at those results and look at the totality of the data that exists.

But currently, we have no plans to seek an indication for retinopathy at this time. But when we're discussing the overall benefit risk of Trilipix, and in the context of ACCORD Lipid, we feel that this is an important component of the benefits side of the equation that needs to be fully explored.

DR. GOLDFINE: Thank you.

We're going to move onto the open public hearing session.

Okay.

DR. CHOWDHURY: Dr. Goldfine?

DR. GOLDFINE: Yes?

DR. CHOWDHURY: (Inaudible – microphone off.)

DR. XU: Yes. My name is Nancy Xu. I'm from the Division of Cardiovascular Renal Disease

Products. And I did a review to address the question, what does the elevation in serum creatinine and the reduction in albuminuria represent in fenofibrate?

So as you know, the data on the mechanism of fenofibrate's renal effects are limited. However, there are animal studies suggesting that fenofibrate might have effects on renal hemodynamics. That's Wilson in 1995.

So with the assumption that these effects are also true in humans, then you expect a decrease in GFR, of course, and translating to an increase in serum creatinine and a decrease in excretion of album in the urine, which these findings are consistently seen in clinical trials.

So because these findings are very transient, they dissipate off therapy. We do not feel, at this point, based on the data that we have seen, there is any compelling evidence of renal protection.

I want to know if there's any other questions I can address at this time.

DR. GOLDFINE: Thank you. And do you think there is renal toxicity?

DR. XU: Right. So based on the summary presented -- and I have not reviewed subject-level data. So what we're seeing is a mean serum creatinine between the placebo versus the fenofibrate group. Over the course of the therapy, they stay relatively constant. And right after therapy, there's essentially no difference at one single timepoint in one subgroup. And based on the report, there is no significant detectible change in the incident rate of end-stage renal disease or doubling of serum creatinine.

So based on these findings, I would say these studies did not detect, overall, a significant safety concern.

I do want to raise the issue of, if it's true this is a potential hemodynamic effect, then some considerations might be given to what dose of fenofibrate one might use in patients who are conceivably dependent on renal alter regulation for renal perfusion. Such patients might be people who

are volume depleted or who are also on other meds that caused changes in renal alter regulation.

Open Public Hearing Session

DR. GOLDFINE: Thank you.

All right. Now, we will move onto the open public hearing portion of the session.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing of the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with a sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance to this meeting.

Likewise, the FDA encourages you, at the very beginning of your statement, to advise the committee if you do not have any such financial relationship.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, speak only when recognized by the chair, and I thank you for your cooperation.

Our first speaker is Diana Zuckerman.

DR. ZUCKERMAN: Thank you. I'm Dr. Diana

Zuckerman. I'm president of the National Research Center for Women and Families. And our non-profit center does not accept money from pharmaceutical companies, and I therefore have no conflicts of interest.

My perspective is as someone trained in epidemiology at Yale Medical School. I was on the faculty at Yale and Vassar, conducted research at Harvard before coming to Washington about 25 years ago, where I've been working on health policy issues. And our center is dedicated to improving medical treatment for adults and children.

In that respect, I have observed more than 100 FDA advisory committee meetings, and I only speak when we think that the evidence is strong enough that we have a clear and strong opinion about what the data are showing. We're really focused on the data. And we know from the work that we've done that FDA's standard is for proving -- that the sponsor is supposed to prove safety and effectiveness. And sometimes, it's hard to distinguish between proving and wishful

thinking.

We all know that heart disease is a terrible problem in this country for men and women. And we want to reduce the harm that it does, but we can only do that if we look at the science and figure out what the science is going to tell us.

So in that light, I wanted to focus on the fact that there is no evidence that the combination therapy is effective for women. In fact, the evidence is going in the other direction. I'm sorry I don't have a PowerPoint, but in the questions and comments, you can see right there that the significance level for the interaction for men and women for the combination therapy being detrimental for women versus some possible effectiveness for men was significant at the .01 level. And that is I think the highest significance level of the data that you've looked at, for the most part, today.

So there's some trending of some evidence of effectiveness for men or for some men, a subset of men, but the evidence for women is actually much

clearer. There's just no evidence that the combination therapy is helpful to women, and some evidence that it may be harmful. So I don't see how it could be a good idea to continue to have this combination therapy be considered an approved use for women.

For men, the data is much more confusing. It may well be that some people or some men do benefit, but the sponsor has not really proven that. And as has been discussed, there is some evidence that it may be helpful. There is some evidence that may support the hypothesis, but you've got a bunch of studies, and the evidence is not clear that combination therapy does improve safety or effectiveness for men or even for a subgroup of men.

So I'm just asking you today to consider the data. I'm sure that there are some patients who will seem to benefit from combination therapy, but that doesn't mean they really are benefitting. That's why we have clinical trials, to distinguish between the fact that some people get better and

some people get worse. And the whole point of clinical trials is to look at it objectively and figure out if there is clear statistical and scientific evidence of improvement, that it is safe, and that it is more effective than placebo. And we just don't have that today.

So as you consider the questions, I hope that you will absolutely support the idea of more research. We need more research and we need some better subgroup analyses. It would be very helpful to have more people of color in these studies, as well as looking at women and men separately, and the different groups of men and women separately. But in the meantime, we strongly support withdrawing approval. Thank you very much.

DR. GOLDFINE: Thank you, Dr. Zuckerman.

I now call Dr. Tybjaerg Hansen.

DR. TYBJAERG-HANSEN: Good afternoon, ladies and gentlemen. I am Anne Tybjaerg-Hansen. I'm from Copenhagen University Hospital. My travel here was paid for by UPM Pharmaceuticals.

I'd like to share with you some data from

the Copenhagen City Heart Study observational data from a perspectives study of the general population. Now, some of the main differences from the ACCORD study are shown on this slide up there, and I'll just share with you a few points.

First of all, we measured non-fasting triglycerides as opposed to fasting triglycerides in the ACCORD study. And non-fasting triglycerides may be better markers for cardiovascular risk. We also, because our hypothesis was that high and very high levels of triglycerides would predict risk of cardiovascular disease, categorized the triglyceride levels into low levels below 1 millimole per liter or 90 milligrams per deciliter, and then in increments of 1 millimole per liter up until at or above 5 millimoles per liter, or at or above 440 milligrams per deciliter. Now, this was not done in the ACCORD study, but you have heard a lot about the subgroups today.

Down below, I can't really see it, but this is events in women. In the two studies, we had 700 incident myocardial infarctions, 750 ischemic

strokes, and 3,700 -- I can't see the number, actually -- total deaths, whereas the total number of events in the ACCORD study was 133.

Now, just as LDL can pass from plasma into the intima, and some of it may get trapped there and cause atherosclerosis due to the cholesterol content, non-fasting triglycerides are a marker of triglyceride-rich lipoproteins or remnant lipoproteins. That is, chylomicron remnants and VLDL remnants. And these larger particles can enter into the arterial wall, get trapped there, and they are also atherogenic, and this may be due to their cholesterol content. So non-fasting triglycerides mark the presence of remnant lipoproteins, which are atherogenic particles.

This shows remnant cholesterol as a function of non-fasting triglycerides. And as you can see, non-fasting triglycerides are an excellent marker for remnant cholesterol and the numbers you can see at the bottom of the slide.

This is the cumulative incidence of myocardial infarction in women in the Copenhagen

City Heart Study as a function of age, and stratified by low, intermediate, and high levels of triglycerides. And as you can see, for any age, the cumulative incidence of myocardial infarction is highest in those with the highest triglyceride levels. And, for example, for the age of 80, the incidence is 5 percent in the low group versus more than 40 percent in the high group.

This is the hazard ratio for myocardial infarction as a function of triglyceride levels, women at the top, and men at the bottom, and adjusted for age to the left. And as you can see, there's a step-wise increase in triglyceride levels in both women and men as a function of triglycerides. And in the highest group, the hazard ratio is about 16 in women and about 5 in men. And when we adjust multifactorially for all other cardiovascular risk factors, then risk is somewhat attenuated. If we look at total mortality, this shows more or less the same in women. The hazard ratio in the highest group is around 5 for total mortality. It's around 2 in

men, and it's not much attenuated.

The last two slides compare non-fasting cholesterol and non-fasting triglycerides as markers. And you can see that for myocardial infarctions, triglycerides are a better marker in women. And in cholesterol, it's also a better marker for mortality, whereas in men, cholesterol to the left is a better marker than triglycerides for myocardial infarction, but triglycerides are still a better marker for total death.

This is my summary slide. Non-fasting triglycerides mark the presence of atherogenic remnant lipoproteins that are associated with increased risk of MI and mortality in both women and men, but they are better predictors of MI and mortality in women than in men and are better predictors of MI and mortality than cholesterol in women. Thank you.

DR. GOLDFINE: Thank you very much.

Our final speaker is going to be Dr. Brinton.

DR. BRINTON: Thank you for the opportunity

to speak. I am conflicted in that my expenses and honoraria have been paid by Lupin, which markets Antara. I have a prior conflict with Oscient, who marketed Antara, as a speaker for them. I have a conflict with Abbott as a recipient of a grant, a research grant, and a speaker, and consulting honoraria.

I'm also conflicted as a speaker and consultant for CoA Pharmaceuticals, who also market a fenofibrate, Lipofen, and conflicted with the GSK, which markets a competing product, which is triglyceride-lowering, Lovaza.

I have 27 years' experience as an academic lipidologist, diabetologist. I'm a fellow and officer in the American Heart Association, fellow and officer in the National Lipid Association, a founding board member and officer of the American Board of Clinical Lipidology.

We have certainly heard about the importance of hypertriglyceridemia as a risk predictor, and I think especially eloquently, the prior speaker. Fenofibrate has certain uses that I think are less

controversial than others that, obviously, we're debating here today. Safety, I believe, is reasonably well-established. Lipid-lowering efficacy, including for the remnant particles we just heard about, I think, is established.

With regard to CVD efficacy, in a minute, I'll talk about the evidence among the various studies. But specific to women, I would respectfully disagree with Dr. Zuckerman. The .01 was an interaction between men and women, which showed that women were different than men, but the nominal p value for women was not statistically significant. So there was not a statistically significant increase in cardiovascular events in women in ACCORD Lipid. Also, there is no plausible mechanism that I am aware of for a gender difference, and there's no precedent for such a difference.

Microvascular disease I think is very important. I'll talk about that in a minute. My conclusion is that the ACCORD Lipid results should not be interpreted to restrict fenofibrate as a

reasonable option for any individuals who are either women or who are taking statins with a triglyceride of 200 to 500.

This slide simply reminds us of the importance of triglyceride as a risk factor, more so in women than in men. There is a difference with adjustment, but you have to remember that HDL and triglycerides being reciprocally related, adjustment for the one in the face of the other may not be appropriate.

There is a several-fold increase in risk of small dense LDL as one goes from a triglyceride of 100 to a triglyceride of 200. And I think this is important to point out as we're talking about triglycerides above 200. And small dense LDL are pro-atherogenic, more so per particle than larger particles because they slip into the sub-endothelial space more readily. They're more readily retained. They're more readily oxidized. And they are less well-cleared by the LDL receptor, in essence, a down regulation of the LDL receptor. Also, triglyceride-rich lipoproteins, when

lipolyzed, produce free fatty acids, which are both pro-inflammatory and pro-oxidative.

This is a slide you've seen before, but I would point out that, to me, as a lipid scientist, I find this consistency actually reassuring rather than troubling, because it's across several different study designs with different fibrates, which although they may differ in certain minor aspects, are actually very similar in terms of their lipid effects. And, to me, to see the similarity and the consistency is actually evidence of a robust finding rather than a less convincing finding. None of these are definitive by themselves. I think together, they are not definitive, but to me it is consistent, suggestive, and I think important.

With regard to microvascular disease, we've heard a lot about this. I would point out that a very robust and very clinically important endpoint, amputation, foot amputation, was reduced by 47 percent with fenofibrate use. And I think, in our quest for clinically meaningful endpoints, I

think this is one that has been not discussed sufficiently. There are many mechanisms for these microvascular events.

The time course here, in 2001, 2004, we have guidelines saying consider use of fibrates or niacin with low HDL, high triglycerides. This was, I think, supported by FIELD and ACCORD subanalyses in 2009, 2010. Last month, the AHA came out with a scientific statement, focusing in part on triglycerides 200 to 500, highlighting appropriate diet and lifestyle. But then, if diet and lifestyle failed, the statement then says we do nothing.

As a lipid clinician, I don't like that. I prefer the European Atherosclerosis Society statement, which came out 11 days later, saying yes, fibrate and niacin can be considered. I think that's a much smarter thing, since 80 to 90 percent of the patients fail diet and lifestyle. And this just shows the actual algorithm from that set of guidelines.

So I would say that we have some suggestive

evidence for benefit. It's not definitive. I would support a trial, but in the meantime, while we're waiting for seven to eight years to get the trial evidence, I would suggest that we not restrict fenofibrate in women or individuals who have high risk.

DR. GOLDFINE: Thank you very much.

At this time, the open public hearing portion of the meeting has now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. However, we are going to take our afternoon break at this moment.

I would like to invite people to be back in 10 rather than 15 minutes, even though we are running a little early, because we have some international flights that our members need to take, and it would be nice if they stayed for the whole discussion. Thank you.

(Whereupon, a recess was taken.)

Discussion/Questions to the Committee

DR. GOLDFINE: So before we begin the panel discussion, I just want to know if there are any other questions from the members of the committee to either the FDA or the sponsor that we should wrap up with?

[No response.]

DR. GOLDFINE: We will now begin the panel discussion portion of the meeting. Although this portion is open to the public observers, public attendees may not participate except at the specific request of the panel.

The first question for discussion, we've been asked to discuss interpretation of the primary efficacy results from the ACCORD Lipid, specifically as they relate to Trilipix indication for coadministration with a statin.

So we'll start with Dr. Hiatt and come around.

DR. HIATT: Sometimes, when I come to these meetings, I agonize over how to interpret things and what it should mean, but in this situation,

it's not too difficult. It's a clearly negative trial. I think we're all prone to look at subgroup analyses of negative trials, but we should be very cautious to overinterpret subgroup analyses. And when you go there, the first thing that catches my eye is that this may cause harm in women and may associate with benefit in men. And that may or may not be true, but the only way to know that is to study something properly designed.

The subgroup on the dyslipidemic population is less convincing for me, and I think there's some numeric trends of harm that are anticipated, not the renal ones, but the other ones we've spoken about. And so the net benefit to risk on cardiovascular events from ACCORD is unfavorable.

DR. GOLDFINE: Dr. Brittain?

DR. BRITTAIN: I have a somewhat different point of view. I guess, if the question is about the indication, which is about relevant to that high triglyceride, low HDL group, then the overall analysis is not the most relevant analysis for that indication. To me, it is the subgroup that has the

dyslipidemia that is the most relevant analysis. So in that sense, I don't feel like that's just any old subgroup. It's a particularly key subgroup, and, again, perhaps the best analysis to answer the indication question.

But I do have a mixed feeling about this because I am worried about the result in women. Even though there is the statement that there's no drug by gender interaction in the dyslipidemia group, the numbers of women in that group are so small that there's no powers to detect an interaction if there is one. So the fact that the results are concerning in the complement to the dyslipidemia group concerns me. Even though we don't see any direct concern in the dyslipidemia group among the women, I don't think we can feel confident about that group because the numbers are so small.

DR. GOLDFINE: Dr. Weide?

DR. WEIDE: Well, I got it right, because they're both right. And that's because I do think it is the subgroup analysis that is important.

That's the indication. I do think it's highly suggestive that the other studies with subgroup analyses suggest protection. On the other hand, we are comparing apples and oranges, which while they're all fruits, doesn't make me real happy about guaranteeing a result. And the other thing about the women and whether there's harm, that's just so underpowered, it's just totally unreliable. That's an easy assessment.

What does that all mean? Well, what it means is, in my view, we have no data to change anything, and we clearly need a study that will answer the question. I think those are the easy answers.

DR. GOLDFINE: Thank you.

Dr. Veltri?

DR. VELTRI: I'd like to add onto that. I think it's trying to fit a square peg in a round hole here, because I don't see how this trial, really, has answered any question. There's nothing in there to take away, I think, what the current indication is. But it clearly doesn't answer the

question about the indication and going beyond the indication. I frankly don't know what you can make of this study because it wasn't designed to answer this question.

I think there are some concerns there, but there are confounders. And I think the only way you get a correct answer is to at least ask the right question and design the trial to try to get that answer. So I don't know what to say here. I don't think you can say much conclusively.

DR. GOLDFINE: Thank you.

Dr. Cooper?

DR. COOPER: I think that, in agreeing with the previous speakers, the notion is that this study was part of a diabetes trial, so there were some limitations in what they could do. And so I think that the primary results don't demonstrate a cardiovascular benefit, which is sort of that primary question, for this population of persons.

In terms of the subgroup analysis, we've talked a lot about those. I really consider those to be hypothesis generating and allow us to find

what we should do next to study. My take on the findings of increased benefit for the highest-risk group with high triglycerides in the other studies, if I understood correctly, those are not in coadministration with a statin, and so they don't really inform what I think about coadministration with a statin, which is what this question is being asked of us.

So I would say, in terms of that, there is a hypothesis that should be followed up with more study.

DR. GOLDFINE: Thank you.

Dr. Gregg?

DR. GREGG: Yes. My understanding here was that our charge is not to address the benefit-risk tradeoffs, globally, of the drug, but rather relate it to the specific indication. And when we look at it that way, then I think that we do have to pay attention to the subgroup analyses, even though there are flaws there. And when you do that, I actually look at this, and I see that it actually provides us more information than we had beforehand

about its benefits.

So we might raise the question why it was approved in the first place for that indication, but if anything, I think we actually have slightly more support now than we had before. That would be my take on it. But the question that it does lead me to is the additional subgroup sensitivity analyses that show that baseline statin does make a difference.

I think that actually has bearing on the way the indication should be worded, because that raises the question to me, is this really a drug that is designed for coadministration, or is it a drug that is designed after a statin has failed? And so I think that that would be the question I would raise.

DR. GOLDFINE: Thank you.

Dr. Oakes?

DR. OAKES: I'd like to reiterate the point that.01 p value, which looks very stunning when you look at it for differential effects, is a test of quantitative interaction, whether the numerical

value of affects -- the relative risk of men differs from that among women.

It's not a test of whether there is harm for women. And as pointed out, that would certainly not reach -- a test of that specific hypothesis would not reach anything like that level of significance.

So bearing in mind that this is one of a number of pre-specified subgroup analyses, it's certainly, in my view, not beyond the band of chance. Of course, it still needs to be looked at and examined as closely as possible. And so the information should be provided to people who are considering using or prescribing the medication.

On the general point, I agree. I think, with what most other speakers have said, that this study as it was designed doesn't really answer the relevant clinical question. And so we can either say do we go with the subgroup analyses that it presented that certainly on the face of it, to me, looks quite strong, bearing in mind that they are secondary subgroup analyses -- but they seem, to

me, to be quite strong and consistent. But I think I would come down with the view that in order to verify these, another clinical trial needs to be conducted.

DR. GOLDFINE: Thank you.

Dr. Kaul?

DR. KAUL: Yes. I think subgroup rescues of otherwise negative trials are often unwarranted unless the evidence is statistically convincing and clinically sensible. And I have not seen any statistically persuasive data to suggest that the ACCORD data are statistically distinguishable in any subgroup. There are some important pieces of information, but I don't believe that that information is actionable.

With respect to the gender treatment interaction, it is qualitative in nature, and such types of interactions are seldom reliable or replicable. They are not explained by any pharmacokinetic or pharmacodynamic interaction. They are not congruent with external data such as the FIELD study.

So in such a situation, I think the best estimate of treatment effect within a subgroup is the overall treatment effect, which is a null effect. And the same applies to the dyslipidemic subgroup as well. I think it provides us with information, as the previous three other trials, to finally goad us to doing the right thing and validate this hypothesis.

DR. GOLDFINE: Thank you.

Dr. Weide?

DR. WEIDE: Yes. I just wanted to clarify that, as I understand it, the current indication is to use Trilipix for elevated triglycerides, low HDL, after a statin has failed. So it's exactly what the subgroup analyses seem to indicate. So, again, the indication fits the limited data we have at the present time.

DR. COLMAN: Can I just make a slight modification to that?

DR. GOLDFINE: Yes.

DR. COLMAN: We should show the wording, actually, if we could get it up there.

Anybody have it handy?

DR. GOLDFINE: Can somebody please put up the current verbiage for the indication with the statin?

DR. COLMAN: It's just a minor clarification.

So it says to be used in combination with a statin to reduce TG and increase HDL, but we don't specify what level of TG or HDL you have to be at in order to take Trilipix. In other words, we don't say you have to be on a statin, you're at LDL goal, and your TG at that point needs to be above 200, and your HDL needs to be below 35. It just says, you can use this to lower your TG and increase your HDL. So there's a slight difference there.

DR. SPRUILL: Is this for the patient or provider?

DR. COLMAN: No. This is for the physician.

DR. SPRUILL: Okay.

DR. GOLDFINE: Dr. Gregg?

DR. GREGG: I interpret that wording,

though, as meaning that if I show up at my doctor's with dyslipidemia across all markers, then he or she could put me on a statin and fenofibrate simultaneously just at that point. And that's really not what the -- as I understand it, what the ACCORD Lipid trial is --

DR. WEIDE: But it says on optimal statin, who are on optimal statin therapy. So that means it's an adjunct and an add-on. So it doesn't say start them together.

DR. COLMAN: And I would add that because we don't have specific values for TG and HDL -- and I think the consistent finding in terms of a larger treatment effect is seen when you cut the data at TG above 200 with an HDL below 35. A TG over 150 is considered high by many people; I think even now maybe above 100. And an HDL in a woman below 50 could be considered low. So there is a lot of room here for interpretation.

DR. GOLDFINE: Dr. Hiatt and then --

DR. SPRUILL: I had a question. I'm sorry. I was just going to follow up with the FDA person.

On the indications, we have to assume, then --

MR. TRAN: Can you leave the slides on for us?

DR. SPRUILL: -- that patients are on optimal statin therapy. We have to make that assumption.

DR. COLMAN: Correct.

DR. SPRUILL: That's a big assumption, yes.

DR. COLMAN: Right. We wrote that with that intention in mind, that people should first be on LDL. For most people, it's the initial target. If you get to goal, then you have problems with TG and HDL, then you can think about this. So we try to construct it to reflect that practice.

DR. SPRUILL: Okay. I just think that's a large assumption to --

DR. COLMAN: Well, okay.

DR. GOLDFINE: Let's keep it moving because Dr. Hiatt is next.

DR. HIATT: So the disconnect for me is I look at that indication, and it tracks with the

historical criteria for approving metabolic drugs by this division, which is numeric benefit on surrogates that are assumed to have clinical relevance and clinical benefit.

Now, the additional disconnect in the first question is, ACCORD was not testing the hypothesis that a fibrate can lower triglycerides and raise HDL. It was testing the hypothesis that there is clinical benefit to doing that.

So it's hard to resolve whether question 1, whether the ACCORD Lipid trial really informs us about the indication. Well, I guess it does, because the lipids went in the right direction, and we kind of expected that to happen. But the elephant in the room, is that clinically relevant? Is there benefit to doing that?

I think ACCORD, at least in the confines of that particular trial of which we've acknowledged many limitations, is a negative trial. It tells us that in patients with diabetes and some level of dyslipidemia, that additional lipid modification does not have associated clinical benefit.

Now, the hypotheses it generates are very interesting. But in terms of the current label, I'm just struggling because I think we know that these drugs change lipid profiles in ways we assume to be favorable. We know you got it right with the statins, but with other drugs that alter, as you mentioned, HDL and triglyceride, maybe we don't know the answer yet. And so what it doesn't say here is that those changes in lipid profile are associated with clinical benefit. In fact, there is a limitations section that warrants against that.

So that's where I'm struggling. The question on the table is, does the ACCORD trial help us understand the clinical benefit? And I think it does.

DR. GOLDFINE: Thank you.

Dr. Felner? Dr. Veltri next?

DR. VELTRI: If you look at that indication as three prerequisites, A, mixed dyslipidemia, B, either CHD or CHD equivalents, so the type 2 fits there, and then, three, on-statin therapy for the

LDL goal -- if you look at the ACCORD Lipid, the only thing that's clearly there is the type 2 diabetes. There's a subgroup which addresses the mixed dyslipidemia, but that's only a subgroup.

Then for the third prerequisite, and that is on statin, 40 percent were not on statin, and we don't even know whether they would have fit into the guidelines post-statin therapy.

So I think there's some good things there, but there's also some things that make you scratch your head, and I think that's kind of the concern. You're comfortable with the lipid effects, but we have this gender. Is it real? Is it not? I don't know.

So the indication, as it currently reads, I don't think there's anything that you can take away from the indication based on this trial. But you can also -- it doesn't support the ultimate endpoint of clinical outcome based on that indication. You just don't have enough information one way or the other.

DR. GOLDFINE: Thank you.

Dr. Smith?

DR. SMITH: So I generally agree with 98 percent of what's been said. But I think it boils down to clarity of thought and designing a study properly to answer the questions that remain. And perhaps, if we had been around in 2000 -- hindsight is a pretty powerful factor -- we would probably know how to design a better study.

The question is, does the ACCORD study answer the questions that need to be understood in order to make some firm clinically ground decisions? And I would submit the answer is no.

Therefore, we need to take what we've learned at great expense, in energy and in human toil, to design the proper study, to design a study that will take advantage of the nuance that we've gained from all the previous studies, but to design a study that is in keeping with not just the generation of a bunch of numbers for secondary endpoints for which there remain great question in terms of clinical importance, but to get to the heart of the matter.

DR. GOLDFINE: Thank you.

Dr. Brittain?

DR. BRITTAIN: Yes. I guess I wanted to know if the indication, instead of saying mixed dyslipidemia, said the cutoffs that are in the guidelines, that 200 and 40, whatever they are, would you be more comfortable with the results in this trial than the more vague wording that there are now?

DR. GOLDFINE: I'm going to ask the FDA to address that question, but I'm going to say that, from my perspective, to put in these very specific guidelines on a subgroup analysis of a trial that was negative for its primary endpoint makes me a little bit nervous.

So I think that on the one hand, the support of data does suggest that in the patients with the dyslipidemia, there is a consistent suggestion of favorable effects. To actually write that into the guideline and support based on this subgroup analysis is very concerning, but I would like actually to hear the FDA's opinion on that.

DR. BRITTAIN: (Inaudible – off microphone).

DR. GOLDFINE: Can you repeat the question?

DR. BRITTAIN: I guess I was wondering -- I don't know the acronym for the organization that has the guideline of the 200 and 40. The triglyceride above 200, HDL below 40 was I believe an official guideline from some respected entity.

I'm wondering, if that were in there -- I was actually asking the committee, would they feel -- had that been in this indication, would they feel that the ACCORD dataset, not the entire dataset obviously, but the subgroup that's relevant to that pre-defined group from that greater than 200, less than 40, would that make a difference in the interpretation of this question, as opposed to the way it just says mixed dyslipidemia now?

DR. COLMAN: I'm not sure I quite grasp where you're going with your question.

DR. BRITTAIN: No. I was just wondering, if the problem -- my own view is that you can use the ACCORD dataset and do a subgroup analysis that fit with my understanding of the indication, but

maybe -- because I assumed when the indication said mixed dyslipidemia, it referred to something like the above 200, less than 40 from this -- again, I don't know the name.

Is it NCEP guideline? But if that were the case, I was just wondering if people would have a different interpretation of the ability of the ACCORD data to speak to the indication.

DR. COLMAN: I'm not sure if I'm going to answer this the way that you want me to answer it, but NCEP IV will be coming out shortly --

[Laughter.]

DR. COLMAN: -- and they will certainly be taking into account the ACCORD Lipid results, so we may be dealing with a whole different set of guidelines very shortly.

DR. GOLDFINE: Dr. Parks, do you have something?

DR. PARKS: I think I'll just add a little bit of historical perspective. At one point, I believe it was just the statin labels did include information on the NCEP guidelines. The problem

with having treatment guidelines in FDA labeling is that treatment guidelines get updated every five to six years. I mean, FDA labeling would have to be updated as well.

Typically, when we write a label and an indication is granted, it's not just the indication that's in the label; there's a clinical trial section. And the clinical trial section describes the data source supporting that indication. So, for example, if the trial enrolled a certain patient population with a certain lipid profile, that would hopefully be the information that the prescriber can understand from where the benefit-risk assessment was derived, not from the treatment guidelines. Those are practice guidelines for clinicians.

DR. GOLDFINE: Thank you.

I think next, Ms. Killion?

MS. KILLION: I just wanted to indicate my support for the comments that have been made by everybody on the panel, but particularly by Drs. Hiatt, Veltri, and Smith. I think that, from

a patient perspective, the emphasis is not always -- and this is something I was just discussing with Dr. Cooper. The emphasis is not always on the numeric benefit that is indicated, but on the actual meaningful benefit to the patient that is derived.

I think that the information that we've looked at today, that I've read, that we've heard about, and has been discussed, has a lot of exciting hypotheses from a patient's point of view, especially in terms of how it touches on quality of life issues over time with diabetes as a disease.

But what I'm struck by is, at the end of today, or at this point in the proceedings, I feel like what I know is so much less than what I don't know. And I'm not a fan of extracting information from studies that weren't designed to actually answer the questions that we're being asked; I never have been.

So I think that rather than relying on, as Dr. Smith said, the nuance of these studies, with respect to subgroups, we really ought to be

thinking about how do we now move toward actually finding out the answers that these things are suggesting.

DR. GOLDFINE: Thank you.

Dr. Weide?

DR. WEIDE: It's come up a couple times about where the cutoffs are, what it's used for, and stuff. And I would be opposed to putting absolute numbers in. That's just a nightmare. However, unless I am misinterpreting that slide, or I saw it and nobody else did, as I understand, the current prescription writing shows that 90 percent of the prescriptions are actually written for people on statins with triglycerides over 200 or an HDL less than 40.

Now, I don't know every drug out there, but that seems to me probably a heck of a lot better than most of the drugs we write for an actual indication with any data at all. I'm not saying good or bad. I'm just saying, if we're worried about being outside of what the data would indicate, we're already within the data.

So that's come up by a couple people about where we are with that. So I think there were slides to show that. It was a tiny bit lower in women. I think it was 89 percent, and then the other subgroup was 88 percent. But, to me, that's extremely good prescription writing.

DR. GOLDFINE: Thank you.

Dr. Kaul?

DR. KAUL: I had the same comment. I think we have to be very careful about imposing fixed thresholds because different agencies have different thresholds, and it's a moving target. The American College and the American Heart Association came up with a different target. It lowered its threshold, and we've been using 200. I don't know what the ATP 4 will say, so I would caution against that.

DR. GOLDFINE: Any other comments? Or I will try a summary.

Dr. Brittain?

DR. BRITTAIN: I guess that makes me wonder, in a future study, what values you would want to

study.

DR. GOLDFINE: So I think that in summary to this particular question, I think that there was relatively clear agreement that, overall, it was a negative trial, and that adding the fibrate in addition to the statin in this particular group of patients with diabetes, globally, did not show a benefit.

I think, then, there was a lot of concern because the trial was not designed to specifically address the question at hand, and the feeling was it did not succeed in addressing the question at hand because it was not so designed.

That leaves us, then, in a cautious interpretation and potential overinterpretation of subgroups within the particular trial, including very big concerns about either over- or under-interpretation for the group with women, where we were particularly underpowered, and the group who had the more dyslipidemic profile.

I'm going to add in one comment of my own, and that's a particular concern with accepting one

subgroup analysis while rejecting the other one that I think was not mentioned.

I think, then, with that in hand, there was also discussion of the heightened concerns of using surrogate endpoints that are assumed to have clinical benefits, and we've seen this not only in these particular trials, but across other metabolic drugs that we've been looking at, and that there is some reassurance that the use in clinical practice appears to be very consistent with what the findings of this particular trial was.

Unless anybody has anything else to add to my summary, we're going to move onto question 2.

[No response.]

DR. GOLDFINE: Question 2 is, in the subgroup of women from ACCORD Lipid, the incidence of MACE in patients randomized to simvastatin plus placebo was 6.6 percent compared to 9.1 percent in patients randomized to simvastatin plus fenofibrate. And the interaction p value was 0.01 versus men.

Please discuss your interpretation of this

subgroup finding, specifically as it relates to Trilipix indication for coadministration with a statin. And I'll open it for discussion.

DR. KAUL: I think we have already covered this. I mean, they're interrelated, and the emphasis on a p value of .01 is for unadjusted p values. If you adjust it for 10 or whatever number the subgroups are, you will lose that. So it's a qualitative interaction, weak, and I think that it's informative, but not actionable.

DR. GOLDFINE: Dr. Brittain?

DR. BRITTAIN: I think it just, again, adds to the uncertainties about the interpretation. If I had to guess, I would guess it was a chance finding, but I think we have no way of knowing. We cannot tell. And, again, the group of women in the dyslipidemia group is too small to make any real conclusion from.

DR. GOLDFINE: Other comments?

[No response.]

DR. GOLDFINE: No?

All right. It looks like everybody feels

like we've exhausted this particular discussion, and I think that everybody is concerned about a potential signal. Although it is a qualitative interaction and it is weak, one doesn't want to ignore something that's there, but there is great uncertainty in interpreting this. And I think the earlier discussions also did not show this in the FIELD study. So I think that everybody is concerned, and not reassured, but has difficulty interpreting this.

Okay. We'll move onto question 3. In the subgroup of patients from ACCORD Lipid with baseline levels of triglyceride greater than 204 milligrams per deciliter and HDL cholesterol less than 34 milligrams per deciliter, the incidence of MACE in patients randomized to simvastatin plus placebo was 17.3 percent, compared to 12.4 percent in patients randomized to simvastatin plus fenofibrate. The interaction p value was 0.06 versus all others.

Please discuss your interpretation of this subgroup finding, specifically as it relates to the

Trilipix indication for coadministration with a statin. And we will begin with Dr. Weide's comment.

DR. WEIDE: Yes. I just want to say I think we discussed this in great detail.

[Laughter.]

DR. WEIDE: I don't know what more to say. It is suggestive. You can mix apples and oranges, and look at the other studies, but it doesn't give an absolute answer. But, again, I think the first discussion that we had was prolonged and included this.

DR. GOLDFINE: Dr. Hiatt?

DR. HIATT: I think the key point is what Dr. Kaul has already said, that we shouldn't really put more emphasis on one subgroup than another, and you did as well. And I think that's the best thing to do here. We like the idea that a drug works in a positive subgroup, and we kind of want to ignore the fact that the drug may not look so good in another subgroup because we all like things to work, and we don't like things to not work, or

cause harm.

But I think that's a very biased view of these data. So I think the truth is that it's a negative trial, and so all these subgroups are no more convincing that there's harm to women than there is benefit in dyslipidemic patients. But you use those for ways to think about moving forward, but you shouldn't use those to make decisions about patient care today.

DR. GOLDFINE: So I guess I would throw in my interpretation. I agree completely. I raised that comment. But one also then begins to look when one is making a judgment about what else is out there. And I think that the absolute lack of the signal within the FIELD study is a little bit reassuring to the women. And I think that with all the limitations of using different fibrate compounds, with using primary prevention, and secondary prevention, and on- and off-statins, I think the consistency of findings, while being very problematic to try to include in a meta-analysis, is a little bit reassuring that this is more likely

to be true and the other is less likely to be true, but still with the extreme caveat about choosing one and ignoring the other.

I think Dr. Kaul has something to add to that.

DR. KAUL: No. I was just talking about this dyslipidemic -- the dyslipidemic subgroup comprises 17 percent of the overall cohort, but 30 percent of the primary endpoints accrue in this cohort. And Janet Wittes has always cautioned us that we should limit our subgroup analyses to endpoints or subgroups that have sufficient a priori power. And that way, you can limit your spurious findings. And if you just do a rough calculation, that particular subgroup, based on the accrual of events, not the sample size, has about 20 to 30 percent power.

It's a very small subgroup, and in the future, perhaps it will be better served if we avoid such subgroup analyses to make any definitive or jointly definitive conclusions.

DR. GOLDFINE: Dr. Felner?

DR. FELNER: I know that most of us are not as concerned about the subgroup analysis, but if you look at the indication for this drug, at least the combination therapy, at least this follows it. It doesn't go against it, as in, I guess, some of the concern with the female data. But at least it follows it, and so you can at least take that posit away, that it matches what the current indication is.

DR. KAUL: But there are other examples in the literature. I mean, the one that comes to mind is the heart failure trial with amlodipine. The PRAISE 1 trial showed a mortality benefit and failed on the primary endpoint. And the p value was highly significant. The interaction term was significant between ischemic and non-ischemic, and they struggled what to do with it. But the investigators actually followed up on that, and they conducted a PRAISE 2 study. And what did they find? Negative effect.

So subgroup analyses are tempting, but they are treacherous. So I think we have to take

caution.

DR. GOLDFINE: Dr. Veltri?

DR. VELTRI: I think in this particular case, I think what's unusual here is that this is kind of a lipid trial -- and it's not like you're going to do subgroups age, gender, ethnicity, et cetera -- and there was evolving information that was coming out from FIELD with these particular types of subgroups. And I think the ACCORD investigators tried to do the right thing in trying to define a population of mixed dyslipidemia. So in a way, unfortunately, it wasn't totally pre-specified, but there was a landscape around them that couldn't allow that, as well as guidelines changing.

So I just think you'd have to be very cautious, as everyone else has said. But I don't think the intent was bad here. But it's just that, unfortunately, it's led us now to focusing on this subgroup, and it takes away, really, from everything else, as has been alluded to.

DR. GOLDFINE: Other comments?

[No response.]

DR. GOLDFINE: Then in summary, I think, again, it's very similar to what we had already discussed, that the subgroup analyses are always concerning when the primary trial is negative. They suffer from a lack of power, and they're suggestive but without an absolute answer. And the findings are consistent with the other trials, and they are consistent with the currently written indications, but they do not provide full support that is up to everybody's comfort level.

We'll move on, then, to question 4, discuss the safety profile of fenofibrate and fenofibric acid, specifically as it relates to Trilipix indication for coadministration with a statin, and if we could potentially try to focus on the other safety issues that have been raised with the liver, the DVT, and the pulmonary embolism questions, the pancreatitis, and the hepatitis. This would be a good time to focus on the other aspects of safety.

DR. HIATT: I don't want to jump in too quickly here, but I don't think there are any

surprises. The rhab dose signal is, at an absolute risk basis, small, but the relative risk is significant. It appears that coadministration increases that risk. And so I think I try to do the counts that come up in question five about how much harm is potentially associated with the medicine, and how is that offset by how much benefit you're receiving.

The liver toxicity didn't seem to be terribly concerning, and I think that liver failure was not really described. Those are also rare events, typically. We didn't hear about the pro-thrombotic risk, didn't discuss that very much, so it would be a little hard to comment on that.

So I think that, like with any drug and particularly with any drug combination, you wonder if A plus B is worse than A or B, and it may be that the main message I got was the rhab dose signal.

The other thing I raised earlier was, it doesn't seem to be preventing pancreatitis. I'm not going to assume causality in terms of whether

it is truly raising the risk or not, but I do think that we think about very high levels of triglycerides as potentially putting patients at risk for very low risk events. And I realize also that triglyceride values can wax and wane considerably based on diet, and sometimes you reach levels above the saturation kinetics for a drug, and then the levels can go extremely high, and then come back down over time. And is that patient at risk for pancreatitis?

These trials weren't designed to answer that question, but the observational data I found were interesting as much as the clinical trial randomized data. And it doesn't look like it's changing the natural history of pancreatitis here in a favorable direction. It may be slightly unfavorable. It may be something related to the drug, or something in patients; getting those cases have other issues that weren't measured.

So I think the risks are predictable. I think the effect on pancreatitis should be noted, just because I think practice patterns drive a

little bit of physicians' decision making about that particular thing. And the other risks I think were anticipated.

DR. GOLDFINE: Thank you.

Dr. Weide?

DR. WEIDE: The issue with pancreatitis is that most like -- well, by design, the patients at high risk were excluded because you had to have triglycerides of less than 750 to be included in the trial. And we argue a little bit about where the cutoff is that's at high risk for pancreatitis, but certainly, it's above 750.

Now, does that mean you can't get pancreatitis? No. Because you're right, triglycerides go up and down, so you could still do that. If you go to McDonald's, it doesn't matter what medicine you're going to take; your triglycerides are going to go up. But the high-risk population was excluded from the trial. So to make a comment about whether or not it reduces I think is unfair because you ought to have a low hit number anyway.

Clearly, other data in other trials and the other indications for the fibrates are elevated triglycerides over 750, and it does reduce the risk of pancreatitis. So I think we have to take that into account.

DR. GOLDFINE: Dr. Veltri?

DR. VELTRI: I think this data is actually reassuring that there's no new signal. This is a large database of concomitant lipid treatment here with statins and fenofibrate. So I think, from that perspective, follow-up for 4.7 years on the average. So I think that's very reassuring, actually, from a safety perspective. There's no new signals.

Actually, the pancreatitis, as was alluded to, these levels, the triglyceride levels aren't that high. But they're potentially competing risks here as well. Fibrates can increase biliary cholesterol. Statins may decrease biliary cholesterol; some pancreatitis in the hepatitis cases. I don't know. That could have been gall bladder related. But it didn't look like -- when

you looked at the statin with the fenofibrate, or the fenofibrate alone, the odds ratio was still about 2 and a half. So I look at the safety as really more reassuring than anything else.

DR. GOLDFINE: Dr. Gregg?

DR. GREGG: Just a comment that I would agree with that last comment, that the absolute risks that we're seeing are reassuring. And if we were making a judgment about the initial approval of this, we probably wouldn't even have as much of the benefit of the observational data at all. We'd have to make this decision based on perhaps the trial data and smaller numbers, on Phase 3 information. So I feel actually comfortable about that.

DR. GOLDFINE: Any other comments?

[No response.]

DR. GOLDFINE: Okay. So I will try to summarize it. I think everybody felt that there was some reassurance that there no new signals of safety that were brought up in the trial and felt that the years of observational data was concordant

with this and also somewhat reassuring.

The acceptable absolute risks, because what was actually uncovered was relatively small, although there is a little bit of a relative risk increase of rhabdomyolysis, it was small and the others were too infrequent, or the data to support actual causality was insufficient for additional comment.

So for question 5, discuss the benefit-risk profile of Trilipix when used in combination with a statin to reduce triglyceride and increase HDL cholesterol in patients with mixed dyslipidemia and coronary heart disease or coronary heart disease equivalent, who are on optimal statin therapy to achieve their LDL cholesterol goal.

Dr. Heckbert, do you want to start?

DR. HECKBERT: Right. Yes. Thank you.

I think, as has been discussed here, the information that we have talked about today really doesn't shed much light on this question. And so although we may have opinions about this, really, it doesn't come from the ACCORD Lipid trial. So to

answer this question, we really need a trial focusing on individuals with low HDL and high triglycerides.

DR. GOLDFINE: Dr. Weide?

DR. WEIDE: Third version of the same question, I think. So we can all repeat ourselves, but I really think it's the third version of the same question.

DR. GOLDFINE: Does anybody have an additional comment?

[No response.]

DR. GOLDFINE: Okay. So, again, in summary, I think that it has previously been stated, and the information does not shed sufficient insight for the subgroup analyses.

Dr. Colman, you want to comment on this?

DR. COLMAN: Yes. Just before you get to Question 6A and B, as I mentioned earlier, your comments today will influence not only the Trilipix coadministration indication, but also the division's approach to other combinations of statins and fibrates, because we have had companies

interested in gaining approval based on just changes in TG and HDL.

So I'd like you to keep in mind not only how this applies to Trilipix, but what your thoughts would be in terms of the standards that should be applied for approval if a company were to come to us and say we have a fixed-dose combination of a statin and a fibrate, what do we need to do to get approved. So it's kind of an addendum to question 6.

DR. GOLDFINE: Does anybody have any additional questions about the point that was just raised?

DR. WEIDE: Yes. That's a completely different question than we're being asked if you're saying a combo drug. That's not at all what we've been discussing. We've been discussing adding a fibrate after optimal treatment with a statin. So I think that's what we're going to be voting on, and if somebody shows up with a combo, that's going to be a totally different discussion. I think it'd be unfair to put those two together.

DR. GOLDFINE: Dr. Colman, do you want to respond to that?

DR. COLMAN: Well, I guess maybe we shouldn't fixate on the combination, fixed-dose combination; if a company came to us and said, we just want to get our statin and a fibrate co-packaged, or we want a similar indication as the one that Trilipix has. So I guess focus less on the term "fixed dose," and simply another company with a similar proposal, and what you think is a reasonable level of evidence to support approval.

DR. GOLDFINE: Does anybody else want to discuss this? Dr. Kaul?

DR. KAUL: On March 30, 2010, a combo pill was -- I don't know what the FDA's decision was, to hold off or whether it was an outright no to rosuvastatin and fenofibrate combination.

What was the name of the product? Certriad or something? Was that a hold, a partial hold until --

[Dr. Colman nods no.]

DR. KAUL: Okay. Because that might inform.

DR. GOLDFINE: Thank you.

Any other questions?

[No response.]

DR. GOLDFINE: If there are no additional comments, then, we're going to move onto question 6A. Taking into account all relevant data and levels of evidence --

Yes? Dr. Gregg?

DR. GREGG: Sorry. I'd like to ask a question about the implications of this one, if we're actually going to be asked to vote now.

When the statement is should FDA require the conduct of a clinical trial, does that imply, then, that without that trial, that there are some other aspects of the availability or indication that changes, or is that just simply a statement of agreement that there should be a trial?

DR. COLMAN: I think, obviously, the first part of the question will perhaps influence your answer to the second part. But I think, just based on the totality of the evidence that we've discussed today, do you support or do you not

support that first question?

DR. GOLDFINE: Dr. Hiatt?

DR. HIATT: Just another point of clarification. I mean, the current labeling just focuses on the lipid parameters and doesn't really speak to the presence or absence of clinical benefit. And, of course, that is I think the big question in the room today, that at least in my opinion, you should change that standard.

So this question, the way I would like to interpret that is should that become the standard not just for this drug, but for future drugs.

Is that a direction you'd like us to take with that question?

DR. COLMAN: I'm not going to comment on whether I thought what you said was appropriate, but yes. You're right.

[Laughter.]

DR. GOLDFINE: So I think we've had some clarifications on this, so I'm going to read the question. Should the FDA require the conduct of a clinical trial designed to test the hypothesis

that, in high-risk men and women at LDL cholesterol goal on a statin with residually high triglyceride and low HDL cholesterol, add-on therapy with Trilipix versus placebo significantly lowers the risk for MACE? Vote yes, no, or abstain, and provide a rationale for your recommendation.

We will be using an electronic voting system for this meeting. Each voting member has three voting buttons on your microphone, yes, no, and abstain. Please vote by pushing the button located immediately below the corresponding letter. Again, firmly push the same button three times.

[Laughter.]

DR. GOLDFINE: After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. I will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will say their name and vote into the record, as well as the reason why they voted as they did.

MR. TRAN: If you're ready to vote, go ahead and enter your vote. Please push the button. You

don't have to do it three times.

[Vote taken.]

DR. GOLDFINE: I'm going to read the voting results into the record. Yes, 13, no, zero, abstain, zero.

We'll now go around the room so that people can comment on their votes. We're going to start with Dr. Hiatt.

DR. HIATT: William Hiatt, I voted -- we're just going to answer what our vote was? Do you want the justification?

DR. GOLDFINE: What was your vote and your justification?

DR. HIATT: So I voted yes for a clinical trial that had MACE as an endpoint. My justification is that in reviewing the data for fibrates, it is not clear to me if these drugs are clinically beneficial or not. And just to reiterate some of those points, drug choice might matter. Gemfibrozil versus fenofibrate may have different mechanisms. Gender might be a significant response predictor. The early studies

that were positive were men only. The later studies that became more negative included both genders. I think that the baseline lipid values appear to be a response predictor; worse is a better responder. But that's clearly something that needs to be figured out.

Then the question is whether fibrate works as add-on therapy to background statin, so that you have older trials where they were monotherapy and the new trial where it's combination.

The last point I make is, if you were going to try to say to yourself, I'm convinced that fibrates work and the next new fibrate that comes along should be tested against an active control, i.e. a non-inferiority study, obviously, I don't think you can do that.

So I think in some ways I ask myself, how would I answer this question? One way I would say that, is the benefit's still well established, that I know how well fibrate beats placebo; and I'm convinced of that, then a non-inferiority design would make sense to me. But I think there's a ton

of heterogeneity across these different studies. And because of that, and because the most recent one that informs us in terms of contemporary medicine was negative, I don't see any option but doing a trial to try to sort those things out.

DR. WEIDE: I'm Lamont Weide. I voted yes. I think there's some good suggestive data, but I think we're all going to say Dr. Hiatt put it very well. We have some limitations and I would ditto everything he just said.

DR. FELNER: Eric Felner, I voted yes. And I just think there are enough questions; the subgroups, whether we like them or not, to appropriately evaluate the question, I think you need to do a long-term study.

DR. BRITTAIN: This was a closer call for me than the others, but I still think there is certainly uncertainty about where this drug works, and what values at baseline, triglyceride and HDL, it would work for. Even though I think there's a pretty good suggestion now that, at least for men, it probably would work, I'm more concerned about

women. And that's one I would say, in that study, you want to make sure that there are enough women in the study so that the question about the effect in women will be clear.

DR. GOLDFINE: Do you mind just stating your name and your vote for the record?

DR. BRITTAIN: Erica Brittain. Yes.

DR. GOLDFINE: Thank you.

Allison Goldfine. Yes. And I think all of my reasons were also stated by Dr. Hiatt.

DR. SPRUILL: Ida Spruill. I voted yes. I agree with all the comments, but I would like to add that ethnic minorities are underrepresented in clinical trials. That's been evidenced by today. And until we make concerned efforts to increase the number of ethnic minorities in clinical trials, I think we will always have questions about the safety and efficacy of drugs for all patient populations.

So as a consumer representative, I support the clinical trials of high risk. And hopefully, high risk will include other ethnic minorities into

the studies.

DR. GREGG: Ed Gregg. I voted yes. Obviously, we weren't thrilled with having to rely on subgroup data, or secondary data from a separate trial to make this decision. So more data that is available -- or if that were available, that would be great. I'm not sure that the wording of that specific trial is after -- you do the deliberations, if that is necessarily the best trial to do with money available.

My understanding is there are still enough questions about the way lipid-lowering drugs work, particularly in women, that you might choose some different comparisons, and you might focus on women, but a trial of this sort would be a good idea.

DR. OAKES: David Oakes. I voted yes. This was a bit of a close call for me also. I think one way of looking at it would be to say that after looking very hard at the ACCORD data, it really doesn't provide sort of definitive, relevant information, which leaves things exactly as they

are. So why not leave the label as it is?

But I think we do want to move the field forward. We do want to have better trials, better standards in the future, and I think this would be an important step towards that goal.

DR. COOPER: I'm William Cooper. I voted yes. I concur with Dr. Hiatt's statement and also emphatically support Dr. Spruill's statements about inclusion of minority patients.

MS. KILLION: Rebecca Killion. I voted yes. In addition to all the statements that have gone before, which I totally agree with, my underlying reason was, to move beyond the suggestions of benefit and risk, you have to do a trial.

DR. KAUL: My name is Sanjay Kaul. I voted yes. I believe that surrogate outcomes, post hoc analyses, observational studies, which is essentially what meta-analyses are, and subgroup analyses in a null trial should not form the evidentiary standard for regulatory decisions. I think clinical outcomes trump numerical benefit in surrogate outcomes. And for those reasons, I voted

yes.

DR. SMITH: Terry Smith, I voted yes. We need the proper trial performed.

DR. HECKBERT: Susan Heckbert, I voted yes. And I voted that way based on the totality of the evidence reviewed today, as well as the lack of evidence regarding the performance of triglycerides and HDL as surrogate endpoints. And based on those considerations, I believe the FDA should change the standard required for developing an indication for adding lipid-lowering drugs to statin therapy. Change it from a reliance on surrogate endpoints to a reliance on outcome trials.

DR. GOLDFINE: Thank you.

For our second question, it's, which action do you recommend the FDA take regarding Trilipix indication for coadministration with a statin? And for this question, there are three options: allow continued marketing of Trilipix indication for coadministration with a statin, without revision of the labeling; 2) withdraw approval of Trilipix indication for coadministration with a statin; and

3) allow continued marketing of Trilipix indication for coadministration with a statin, with revision of the labeling to incorporate the principal findings from ACCORD Lipid.

You're going to be asked to vote 1, 2 or 3 and provide a rationale for your recommendation.

Does anybody want to see the current wording before we make a vote on this question?

MS. KILLION: Yes.

DR. GOLDFINE: Yes? Okay.

And do you have a comment?

DR. HIATT: Yes. I think Dr. Colman said earlier that number 2 does not mean withdrawing the drug from the market; it means withdrawing that particular indication.

DR. GOLDFINE: Dr. Gregg?

DR. GREGG: Additional question for clarification? When we talk about revising the labeling, that is more than just the statement of the indication. Correct? That's additional information that goes with the drug about evidence in subgroups and such.

DR. COLMAN: Yes. We deliberately left that open ended. So I would ask people to give their thoughts in terms of what information they think should go where and why, if you go that way.

DR. GOLDFINE: Any other questions or comments?

[No response.]

DR. GOLDFINE: Can we see the guideline as it's currently written? Dr. Heckbert also has a question.

DR. HECKBERT: Yes. Thank you. I do have a question.

So if the third indication, which talks about the coadministration with a statin, if that is withdrawn, is the company then able or not able to speak with physicians about using it as add-on therapy to patients already on a statin? Because the other two indications don't specifically talk about that, but then they don't rule it out, either.

So I'm just wondering how that would affect, because it talks about allow continued marketing,

or -- I am wondering about the marketing aspects of the question.

DR. COLMAN: Well, if in fact the indication was withdrawn, regulatorily it was withdrawn, then the company would not be able to advertise and promote the use of that drug with a statin; the company. Physicians could still certainly use it as they saw fit.

DR. GOLDFINE: I'll read the indication as it's currently written. "Trilipix was approved by the FDA December 15, 2008 with the following coadministration indication, an adjunct to diet, in combination with a statin to reduce triglyceride and increase HDL cholesterol in patients with mixed dyslipidemia and coronary heart disease, or a coronary heart disease risk-equivalent, who are on optimal statin therapy to achieve their LDL cholesterol goal."

Any other questions before we remove that?

[No response.]

DR. GOLDFINE: Again, we're going to go back to the voting question about which action you are

currently recommending the FDA to take regarding Trilipix indication for coadministration with a statin: 1) allow continued marketing of Trilipix indication for coadministration with a statin without revision of the labeling; 2) withdraw approval of Trilipix indication for coadministration with a statin; or 3) allow continued marketing of Trilipix indication for coadministration with a statin, with revision of the labeling to incorporate the principal findings from ACCORD Lipid.

Please vote 1, 2, or 3, and then you'll be asked to provide your rationale for your recommendations. There are three buttons on your microphone, vote device, that have been labeled below the buttons with the numbers 1, 2, or 3. Please vote by pushing on the button located immediately above the corresponding number. Again, firmly push the same button three times.

[Vote taken.]

DR. GOLDFINE: I'm going to read the vote into the record. 1, which is allowed continuing

marketing indication for coadministration without revision of the labeling, received three votes; 2, withdraw approval of Trilipix indication for coadministration with a statin, that received four votes; and allow continued marketing of Trilipix indication for coadministration with a statin, with revision of the labeling to incorporate the principal finding from the ACCORD Lipid trial, and that received six votes.

We're going to go around the room, and I'd ask you to state your name and your vote into the record, and then discuss your reasonings.

Let's start with Dr. Heckbert.

DR. HECKBERT: Susan Heckbert. I voted 2, and that is to withdraw approval. I felt I needed to vote that way because that's consistent with what I said earlier, which is that I believe the FDA ought to be moving toward requiring trial evidence based on relevant clinical cardiovascular outcomes for therapy that's added onto a statin, where the goal -- or where the intent of therapy is to increase HDL or reduce triglycerides.

If the FDA isn't ready for that yet, for some reason, I would go with option number 3, but I think the FDA should be moving toward that sort of a requirement.

DR. SMITH: Terry Smith, I voted 2, largely for the same reasons. I just don't see how we can allow this to be an indication for co-therapy if we're acknowledging the lack of good evidence-based -- evidence for it.

DR. KAUL: Sanjay Kaul, I voted for withdrawing approval of the indication for coadministration with a statin for the same reasons. I felt it would be incongruous with the principle of equipoise. Right now, we see a disconnect between the marketing and the evidence. And so if you ask people to be randomized to a placebo arm, and you have an approved indication by the FDA, I couldn't reconcile with it personally. So I felt it was incongruous. The only choice I had was number 2.

MS. KILLION: Rebecca Killion. I voted 1. I could probably have gone with 3. I was debating,

and I might even have been able to go for 2. I found this to be very --

[Laughter.]

MS. KILLION: -- not my usual definitive kind of decision. But I went with 1 because after listening to everything and doing all the reading, I wasn't sure what I knew. I didn't know if I wanted to put something in the labeling that I wasn't sure -- you know, based on subgroup analysis, that I didn't feel was completely reliable. I don't think I wanted to commit to that. And then I was hoping, I guess, with label, if we kept it as it is now, that based on trials going forward, which I hope there will be, we would have something we could do more definitively after we know more.

DR. COOPER: I'm William Cooper. I voted 3 on this. And I really viewed -- I struggled with this. I sort of, in principle, agreed with the three previous speakers who supported withdrawing this indication. And the reason that I went ahead and voted for 3, of keeping indication but adding

additional information, is I viewed this through the lens of sort of what I see as FDA's current regulatory approach. I don't see an immediate shift to requiring the long-range clinical outcomes. So I think that would be a direction to go. And so the reason I moved to that third choice was because of thinking about the current realities.

I think that one thing that might be helpful is including information in the clinical trial section of the label about additional information to help guide providers' decision making, including some of the findings of negative results that would help clinicians in deciding whether this drug was going to benefit their patients or not.

DR. OAKES: David Oakes. I voted 3. I didn't feel there was really sufficient negative information to remove the indication. That would have sent a signal, I think, that this group feels that this medication is used that way is unsafe or is inappropriate. I don't think we have the data at this point to say that, so it would be a

different question if we were starting from a blank state, but we're starting from the present to indication. So I feel that it would not be the right message to withdraw the indication.

I do think that people need to be informed of the risks. And they need to be able to weigh those risks individually, and different people will make different decisions about how important these risks or perceived risks are.

DR. GREGG: Ed Gregg. I voted 3 as well for really similar reasons. The science is not particularly satisfying, but I did this from the vantage point that this is a drug that has an indication that's been approved based on a set of information. And now we're presented with a trial that is not really catered to address this question; required us to go to the secondary data. And when we looked at that, it actually provided more support as opposed to -- support for evidence, positive evidence, rather than actually more harm.

All that said, because the overall science is not great here, I think that there should be

much stronger labeling and perhaps a more specific indication to prevent overmarketing of this to people who are not going to benefit from it, or even have some harm.

DR. SPRUILL: Ida Spruill. I voted 3 as well, and I agree with the comments earlier. The only thing I would add is that the statement gives me hope, actually, because it talks about revisions, and it allows us to revise and an opportunity to add something else in there that's a benefit to the patient and the provider, as well as findings. And I think that's important, and so I voted yes. It was difficult, but I went with number 3.

DR. GOLDFINE: Allison Goldfine, I also voted number 3, and I also had a very difficult time, and was torn between number 2 and number 3. I agree that triglycerides and HDL are surrogate endpoints that have been less clearly clarified at this point in time for their value. But this product came along before the guidelines were changing, and it got to this indication for a

reason, and we have some historical data with us.

I think that we are in a transition period, and that we need to be fair during the transition period, and that while in the future may be required to have a different level of evidence, I think that we are where we are today.

I was persuaded by the consistency across all of the trials that were very problematic in interpretation on the consistency of the findings in the patients with the higher triglyceride and lower HDL, which when I put on my clinical hat and I looked at everything, I thought, would I actually potentially recommend or open a discussion about this with a patient, my answer was yes, I would.

Therefore, while it's very different to do individual risk-benefit counseling versus policy setting, I thought that in the whole setting of what we knew, I agreed that it would be a very negative message that would be very confusing to people to withdraw it at this point in time, given the totality of the information.

So I voted yes, and I hope that there will

be very, very clear written adaptations about the quality of the data, and especially the concern for women.

DR. BRITTAIN: Erica Brittain. I voted 3, and I would say for exactly the combination of reasons that Dr. Gregg and Dr. Goldfine.

DR. FELNER: Eric Felner. I voted 1, and I actually struggled between all three throughout the day. But I think I used a little bit of process of elimination in figuring it out, at least my vote. And I think there really wasn't enough information to at least warrant eliminating or withdrawing the indication, especially when the point came up that I didn't really realize, I think until Dr. Weide brought it up, about 90 percent of the drug use is in those patients who have very high triglyceride levels and low HDL. And that's really who it should be geared for.

I was fearful that if 2 took precedent, then you would lose the benefit of where most patients get treated. So then, of course, I was left with 1 and 3. And 3 seemed like the easy choice there, or

the safe choice, but I think the reality is that, if I made 3 the decision, what would I base the revisions on; for the female data?

I mean, everybody agreed. It seemed unanimously that we are going to do a clinical trial, so we're going to get the proper information the appropriate way. So just like the simple test question, I just knocked off two of the choices and picked one.

DR. WEIDE: You can help me with boards.

[Laughter.]

DR. WEIDE: Lamont Weide. I voted 1. I hope Dr. Kaul will not view me poorly. We usually vote similarly. But I think we think the same, and I think the reason we voted so differently is because I looked at this as already having an indication. And if we say that everything that was presented to us was not definitive, then I don't have any information to change what was already done.

Now, if this was going to be a new indication or a new drug application, I would have

viewed this entirely differently. But I think it already had an indication. And so when I looked at this, I said, have I received any data that is significant enough, that is there, that is strong, that provides me any direction? And the answer was no. So I couldn't take away something that has already been given.

I assume there was other data -- because we just got presented the ACCORD data. Other data was presented earlier at the initial approval of the indication. And unless we want to go through all of that, I can't take away somebody else's decision when they had a different set of data. So I really think we're still together. We're okay.

DR. HIATT: William Hiatt. I voted 2, to withdraw this indication. This indication speaks to me as saying that a high-risk patient who is not yet at target goal should receive an additional drug. And it falls short of saying exactly what's going to be achieved by doing that, but the limitations section suggests that if there's no clinical benefit, that should be noted. Now, we

have a trial that says that we can't learn any new clinical benefit from this.

So I think it's incumbent upon the FDA to make a clearer statement about what the intended use is supposed to be, and I hope that you move past the numbers issue and into the clinical benefit realm. I'd also like to comment on number 3. Doctors don't typically read labels.

[Laughter.]

DR. HIATT: And so if you think that they're going to change their behavior because you changed the label, makes me very nervous. So the only way to really create a sea change in terms of what I think is highly relevant to the practice of medicine in this metabolic area, it should be to base it on proper evidence.

DR. GOLDFINE: I guess at this point, then, we will open it to last words from the division.

DR. COLMAN: Well, I think this was a unique meeting. I think it brought up a lot of different questions, certainly from our standpoint. We don't usually find ourselves in this kind of a situation,

and I hope that we don't again, anytime soon.

[Laughter.]

DR. COLMAN: But certainly, as I always say, I appreciate all of your input and the time you've taken to read the material. I also thank Abbott for all their work, and just thank you.

Adjournment

DR. GOLDFINE: I would actually like to thank all of the presenters, the FDA, for putting together extremely clear information for us. And I would like to thank the sponsor, also, for really an excellent job in putting together the information.

I would also like to personally thank Dr. Ginsberg. I think it was really an excellently conducted trial that was very important in the diabetes realm; and then, of course, all of the panelists for all of their opinions. And with that, I will adjourn this meeting. Thank you for your attention.

(Whereupon, at 4:04 p.m., the meeting was adjourned.)